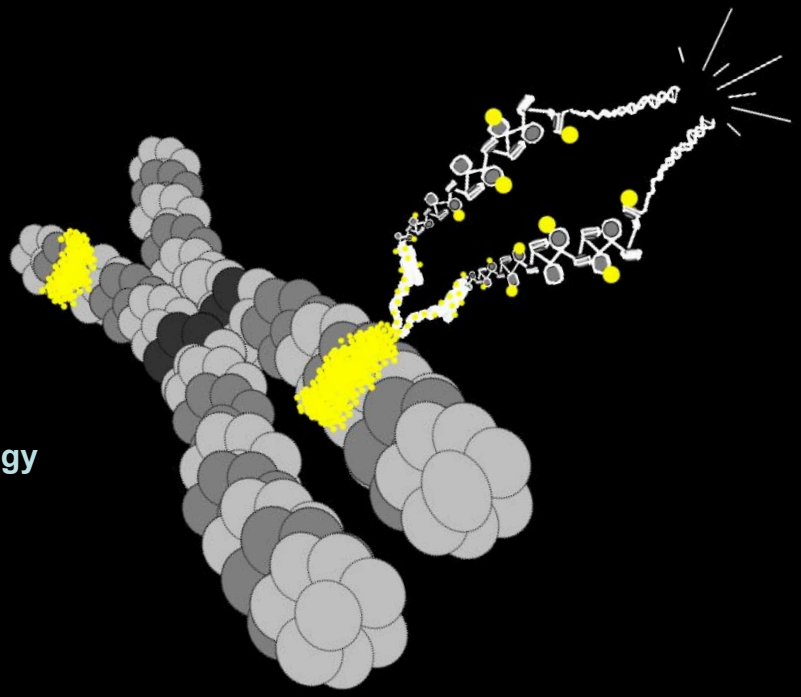
Present and future clinical applications for gamma-H2AX

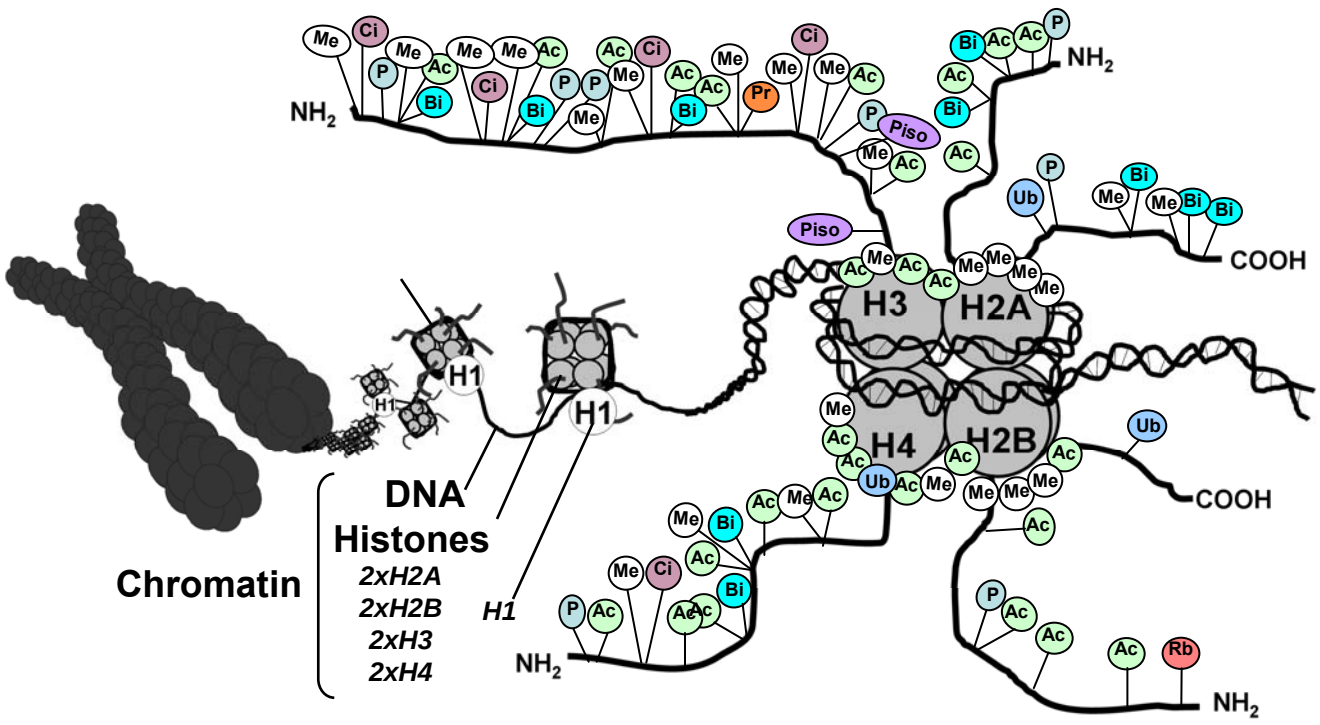


Christophe E. Redon
Laboratory of Molecular Pharmacology
National Cancer Institute, NIH

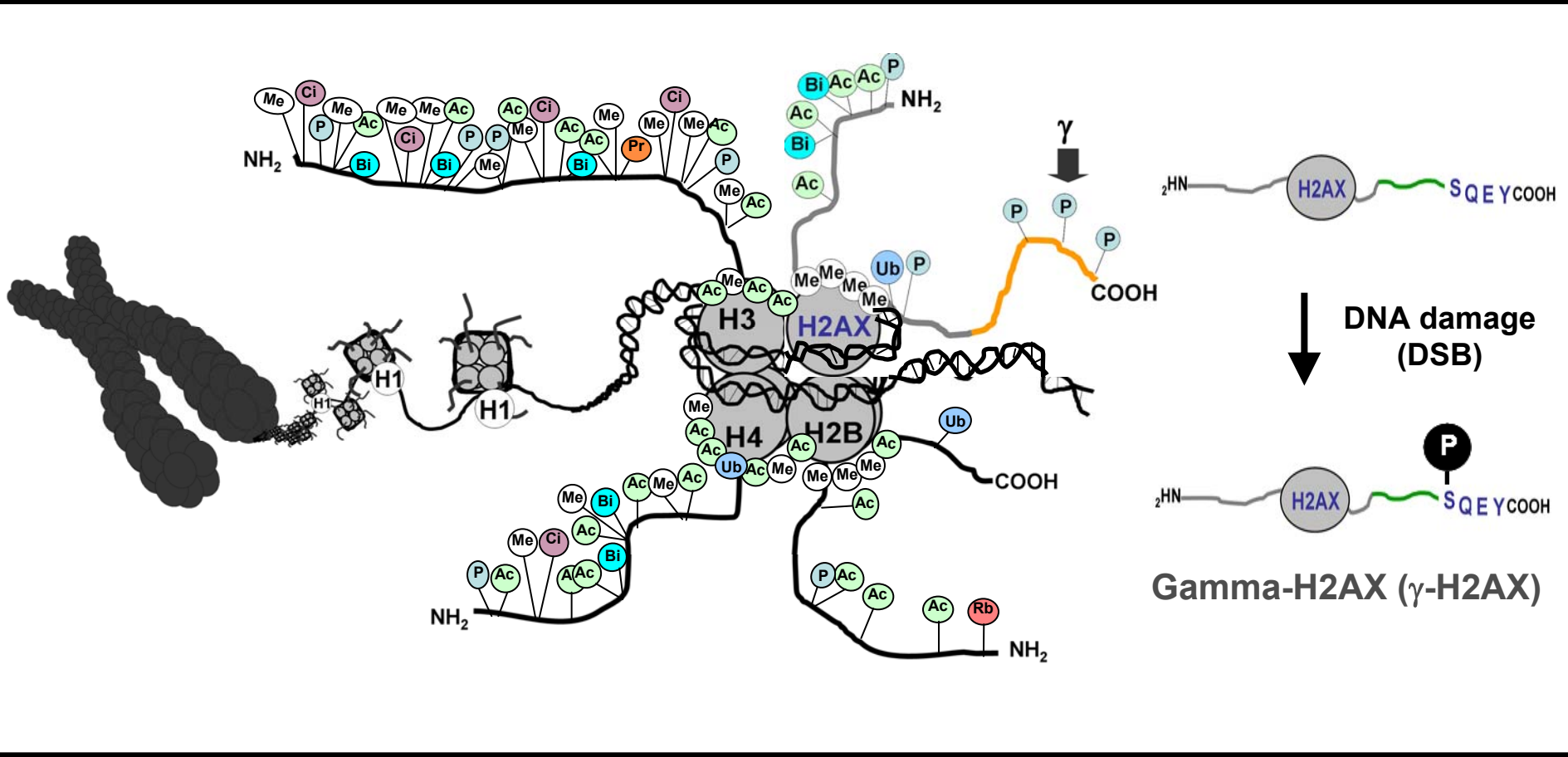
Regulatory Science Considerations for
Medical Countermeasure (MCM) Radiation Biodosimetry Devices Public Workshop

Sept 27-28, 2012

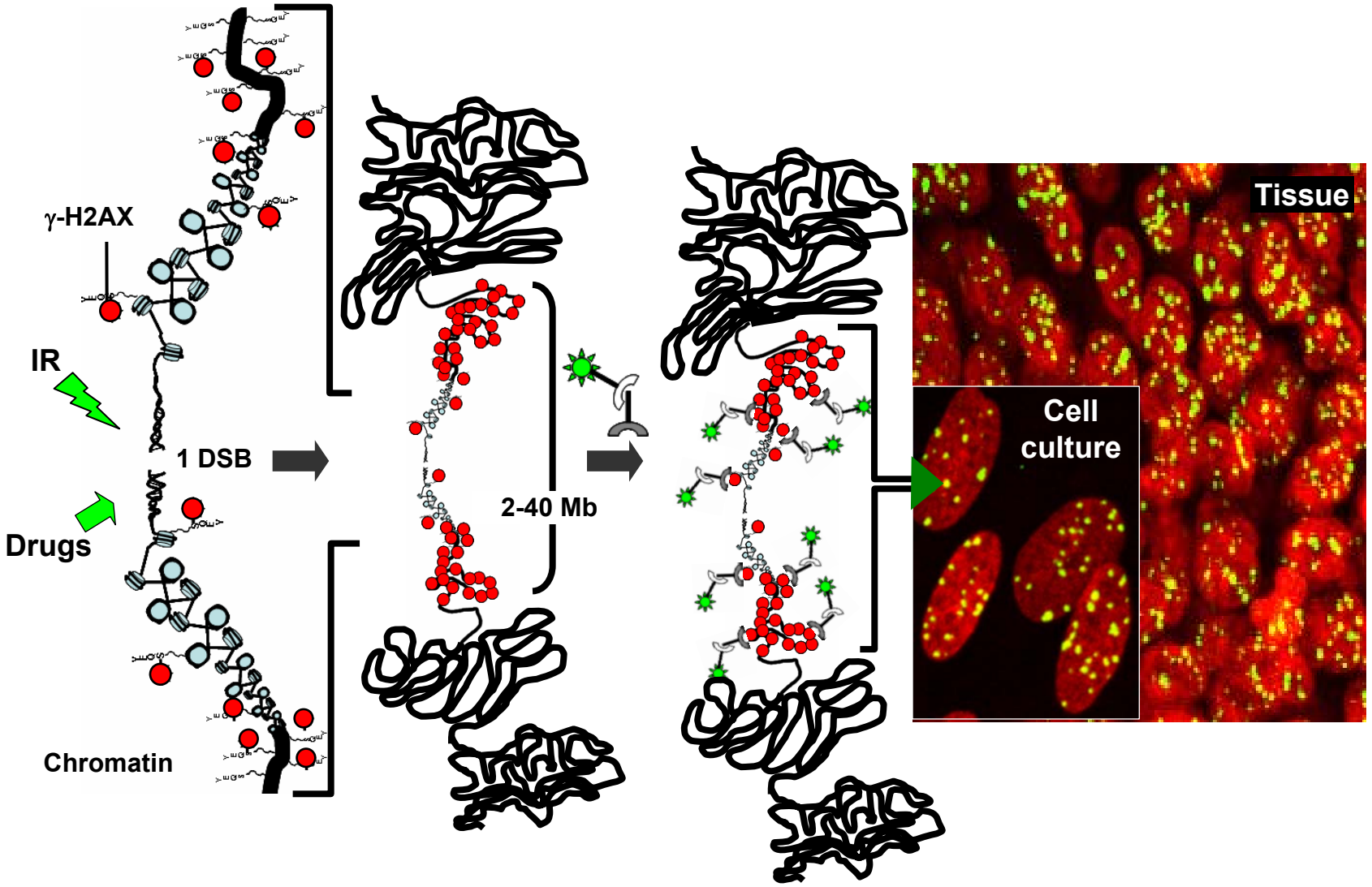
The Histone Code



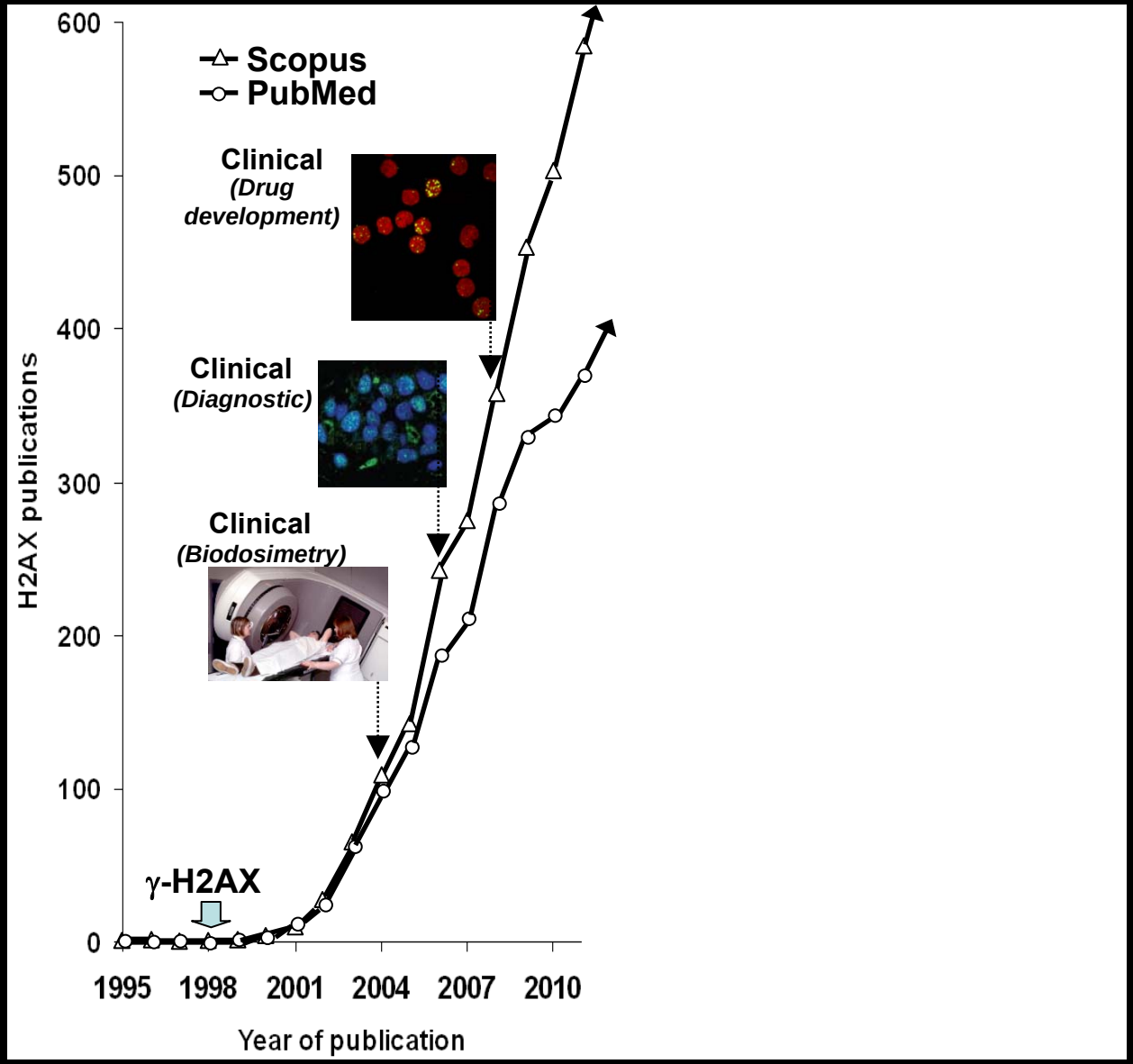
γ-H2AX is a code for DNA damage

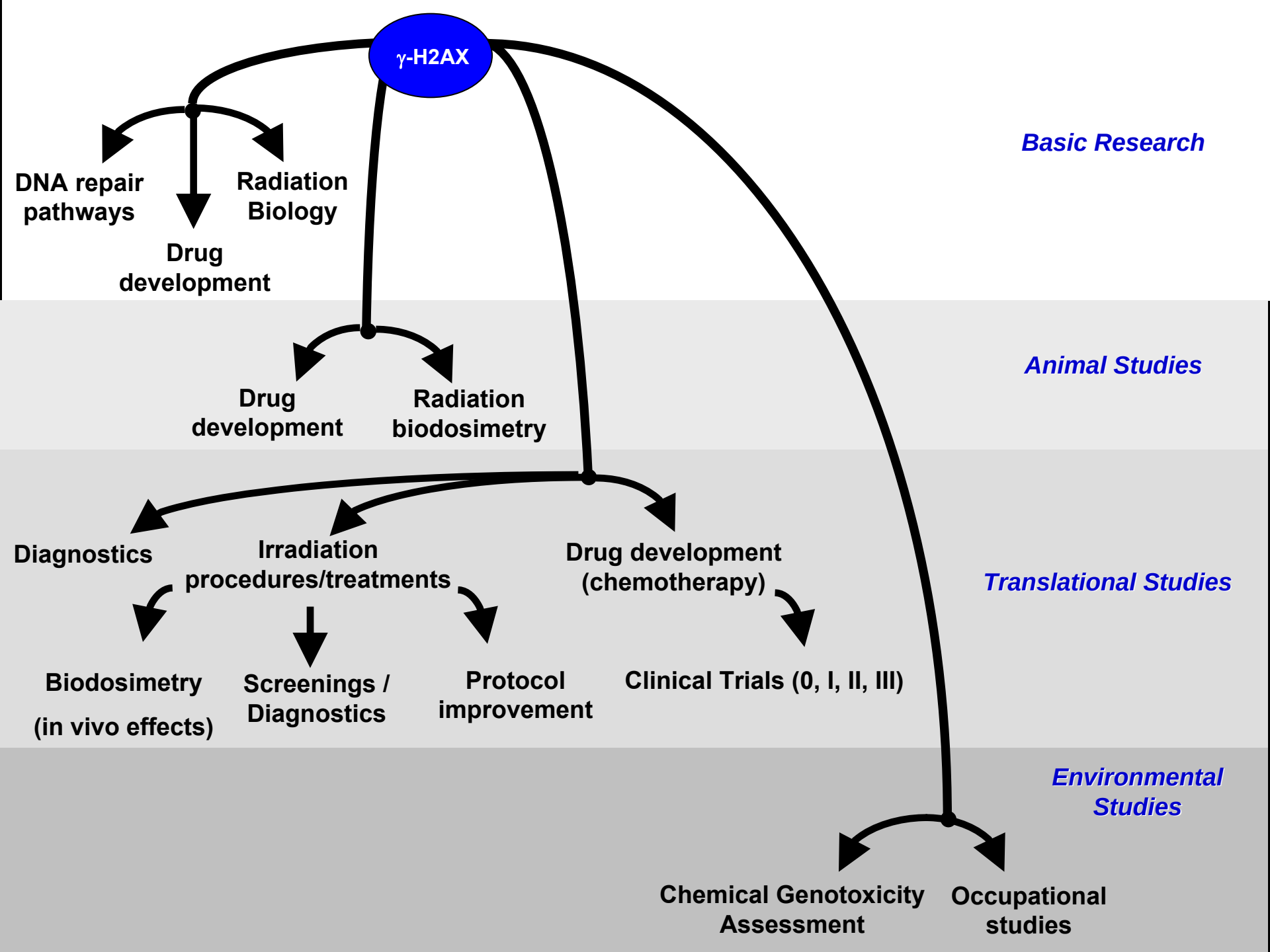


γ-H2AX formation



How important is γ-H2AX?




γ-H2AX
DNA repair pathways
Drug development
Radiation Biology
Basic Research
Drug development
Radiation biodosimetry
Animal Studies
Diagnostics
Irradiation procedures/treatments
Drug development (chemotherapy)
Translational Studies
Biodosimetry (in vivo effects)
Screenings / Diagnostics
Protocol improvement
Clinical Trials (0, I, II, III)
Environmental Studies
Chemical Genotoxicity Assessment
Occupational studies

γ-H2AX

DNA repair pathways

Radiation Biology

Drug development

Basic Research

γ-H2AX and other histone post-translational modifications in the clinic

Christophe E. Redon[1] , Urbain Weyemi[1], Palak R. Parekh[1], Dejun Huang[1,2], Allison S. Burrell[1,3], William M. Bonner[1] *

Drug development

Radiation biodosimetry

Animal Studies

Diagnostics

Irradiation procedures/treatments

Drug development (chemotherapy)

Translational Studies

Biodosimetry (in vivo effects)

Screenings / Diagnostics

Protocol improvement

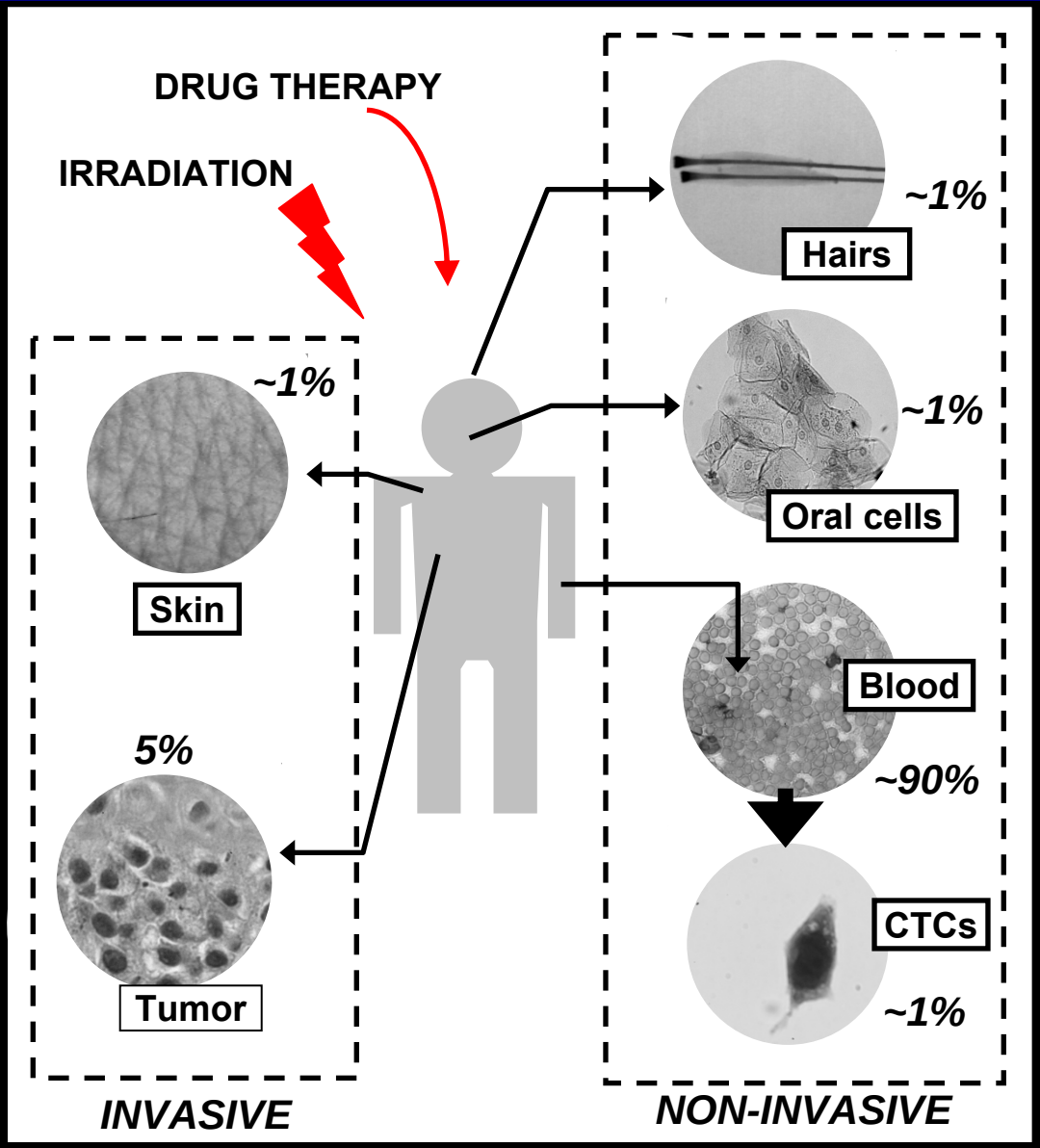
Clinical Trials (0, I, II, III)

Environmental Studies

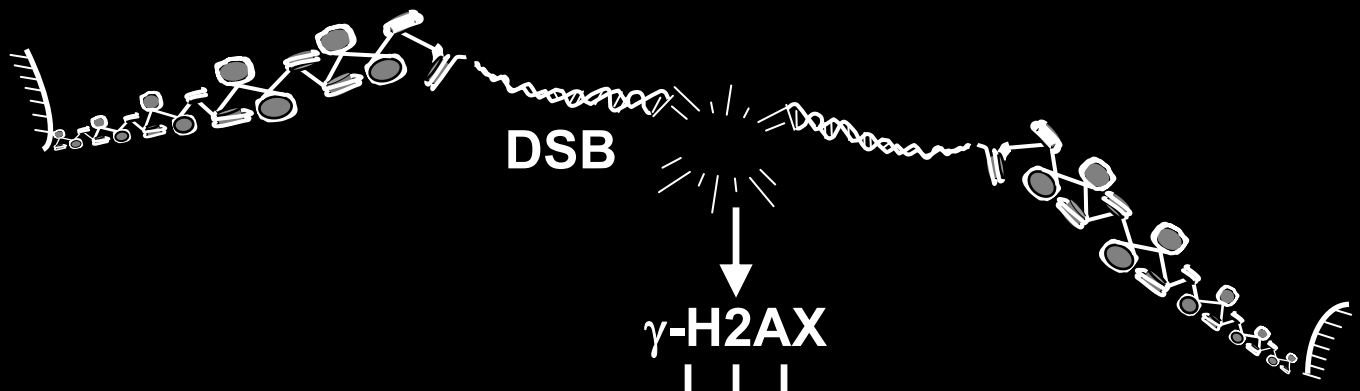
Chemical Genotoxicity Assessment

Occupational studies

Samples used for γ-H2AX detection in the clinic

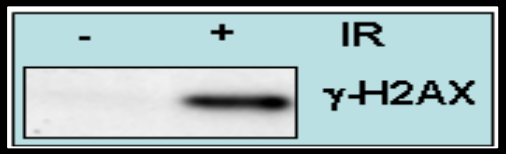


γ-H2AX detection in the clinic



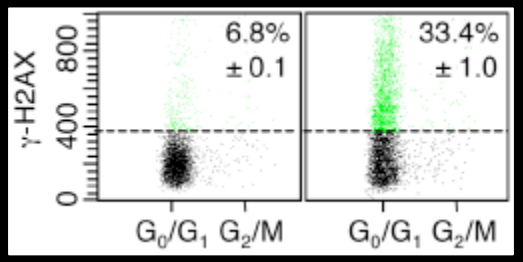
γ-H2AX

Western



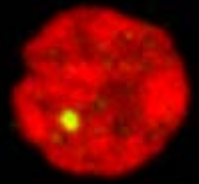
~1%

FACS



~5%

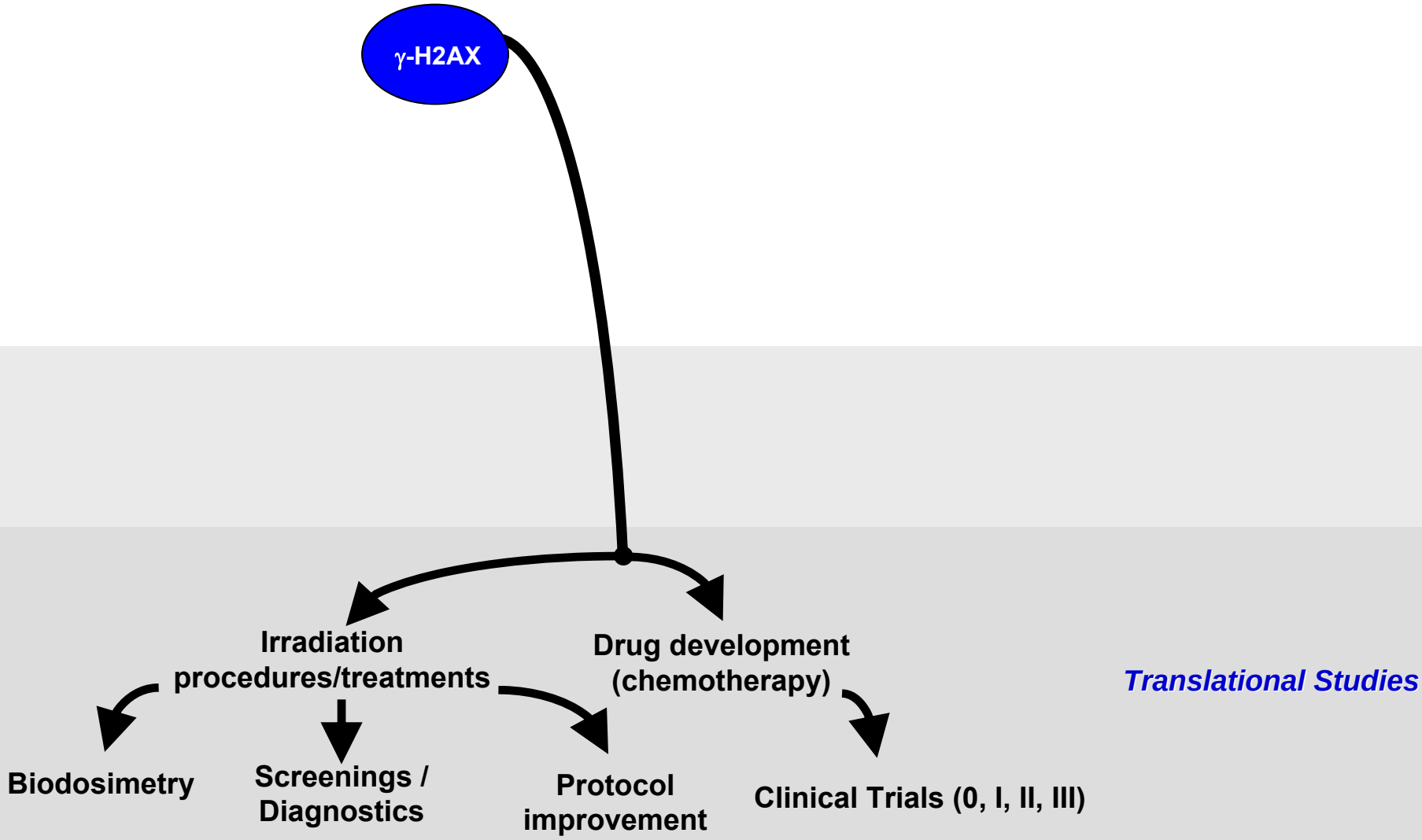
Microscopy



~95%

Detection of a single DSB

γ-H2AX assay is the most sensitive assay to detect / quantitate DSBs



Translational Studies

Why biodosimetry?

Table 1
Non-exhaustive list of clinical studies using the γ-H2AX assay for radiation biodosimetry. Studies are separated in 3 major groups: x-ray examination (top), computed tomography (middle) and radiotherapy (bottom). A study illustrating the use of γ-H2AX as a biomarker to study the impact of space radiation on human health was added in the last row. All studies described in Table 1 used microscopy (i.e., immunocytochemistry or immunohistochemistry) for γ-H2AX detection.

Procedure	Sample	Dose	Study purpose	Ref.
x-ray examination	PBMCs	0.230–0.856 Gy cm (CT) 6.31–30.36 Gy.cm^2 (PTA)	DNA damage evaluation during percutaneous transluminal angioplasty	[123]
x-ray examination	Oral cells	2–3 cGy	Validation of γ-H2AX as a biomarker for low dose radiation exposure	[64]
x-ray examination	PBMCs	10–3170 cGy.cm^2	DNA damage evaluation during pediatric cardiac catheterization	[71]
x-ray examination	PBMCs	337–29,281 μGy .m^2	DNA damage measured after angiographic procedure	[70]
x-ray examination	PBMCs	112–1025 mGy.cm	DNA damage measured after coronary CT angiographic procedure	[124]
CT	PBMCs	157–1514 mGy.cm	Evaluation of DNA damage / repair during CT examinations	[53]
CT	PBMCs	5.16–13.85 mGy	DNA damage measured after multidetector row CT examinations	[125]
CT	PBMCs	200-1800 mGy·cm	To compare the biological effects between helical and sequential coronary CTA as well as other CT parameters	[72]
CT	PBMCs	522 to 1102 mGy.cm (Blood dose 8–20.6 mGy)	To investigate the biological effects of different scanner settings	[52]
Radiotherapy	PBMCs	2–2.17 Gy (SD) 72–76 Gy (CD)	To compare the biological effects (DSBs) of 3D and SSIMRT irradiation protocols to treat prostate cancer.	[69]
Radionuclide therapy	PBMCs	0.17–0.57 Gy	To measure the dose accumulation after administration of (131)I for thyroid remnant ablation	[78]
Radiotherapy	PBMCs	1.6–2 Gy per fraction	Evaluation of DNA damage in different areas of the body after local radiotherapy; Estimation of the applied integral body dose	[67,88]
Radiotherapy	Skin	0.05–1 Gy	To evaluate the low-dose hypersensitivity response in skin of patients undergoing radiotherapy	[126]
Radiotherapy	Skin	~1 Gy	Evaluation of DNA damage induction in prostate cancer patients undergoing radiotherapy	[48]
Radiotherapy	Glioma cerebrospinal fluid	24–30 Gy (CD)	To evaluate the radiotherapy-induced DNA damage induction in glioma cells collected in cerebrospinal fluid CSF cytological specimens	[127]
Space radiation	lymphoblastoid cells	0.7 mSv per day	To evaluate the DNA damage induced by space radiation	[128]

Abbreviations: PTA, percutaneous transluminal angioplasty; SD, single dose; CD, cumulated doses; CT, computed tomography; CTA, computed tomography angiography; PTA, percutaneous transluminal angioplasty; 3D, three dimensional conformal; SSIMRT, step-and-shoot-intensity modulated radiotherapy. PBMCs, peripheral blood mononuclear cells.

few mGy

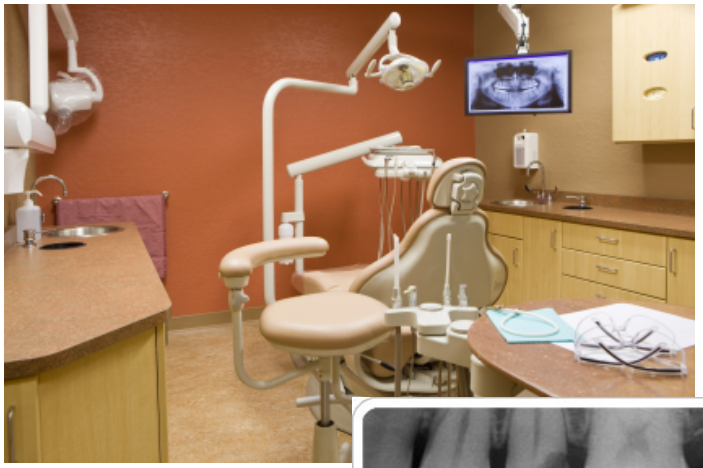
> 70 Gy

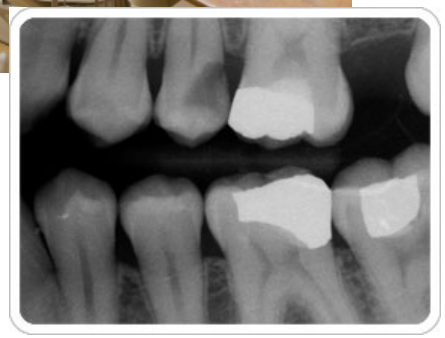
SHORT COMMUNICATION

Expression of Activated Checkpoint Kinase 2 and Histone 2AX in Exfoliative Oral Cells after Exposure to Ionizing Radiation

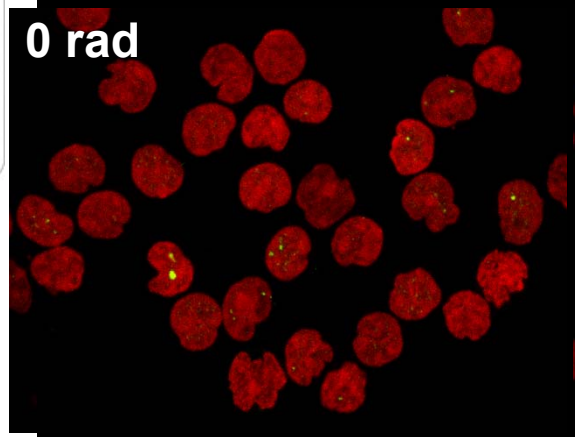
Angela J. Yoon,[a,1] Jing Shen,[b] Hui-Chen Wu,[b] Christos Angelopoulos,[a] Steven R. Singer,[a] Rongzhen Chen[c] and Regina M. Santella[b]

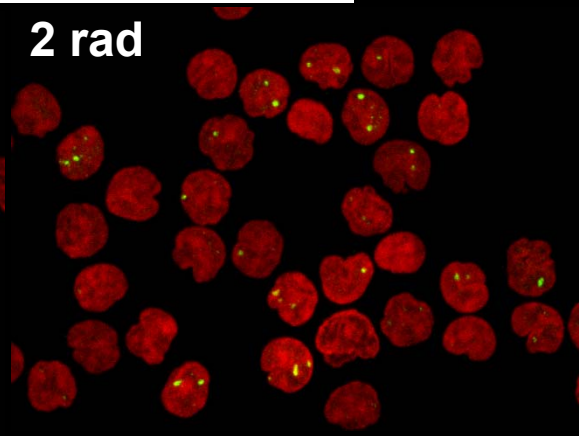
[a] *Columbia University College of Dental Medicine;* [b] *Department of Environmental Health Sciences, Mailman School of Public Health; and* [c] *Herbert Irving Comprehensive Cancer Center, Columbia University, New York, New York*





γ-H2AX (activated histone 2AX) and pChk2 (activated checkpoint kinase 2), which are DNA damage response molecules, are produced in irradiated cells and may be signature molecules of radiation exposure. We investigated their use as potential biomarkers to identify individuals exposed to ionizing radiation. We collected exfoliated oral epithelial cell samples from 100 healthy individuals undergoing routine dental radiographic examination (2.34 cGy) both before and after the radiograph using a non-invasive technique. The expression levels of pChk2 and γ-H2AX in oral cells were assessed by immunohistochemical assay. Both biomarkers showed statistically significant increases in levels of expression after the radiation exposure ($P < 0.001$). This suggests that pChk2 and γ-H2AX may serve as sensitive indicators of low-dose radiation exposure.





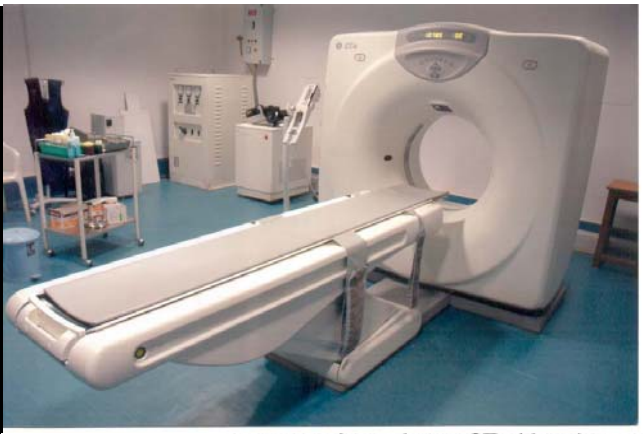
2.34 cGy = 2.34 rad

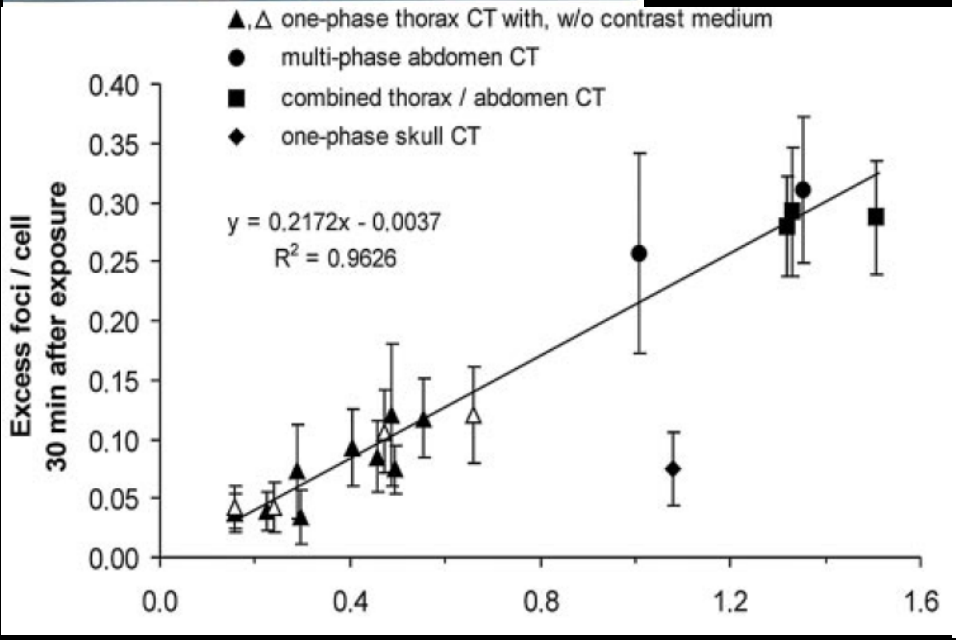
~0.33 DSB/cell

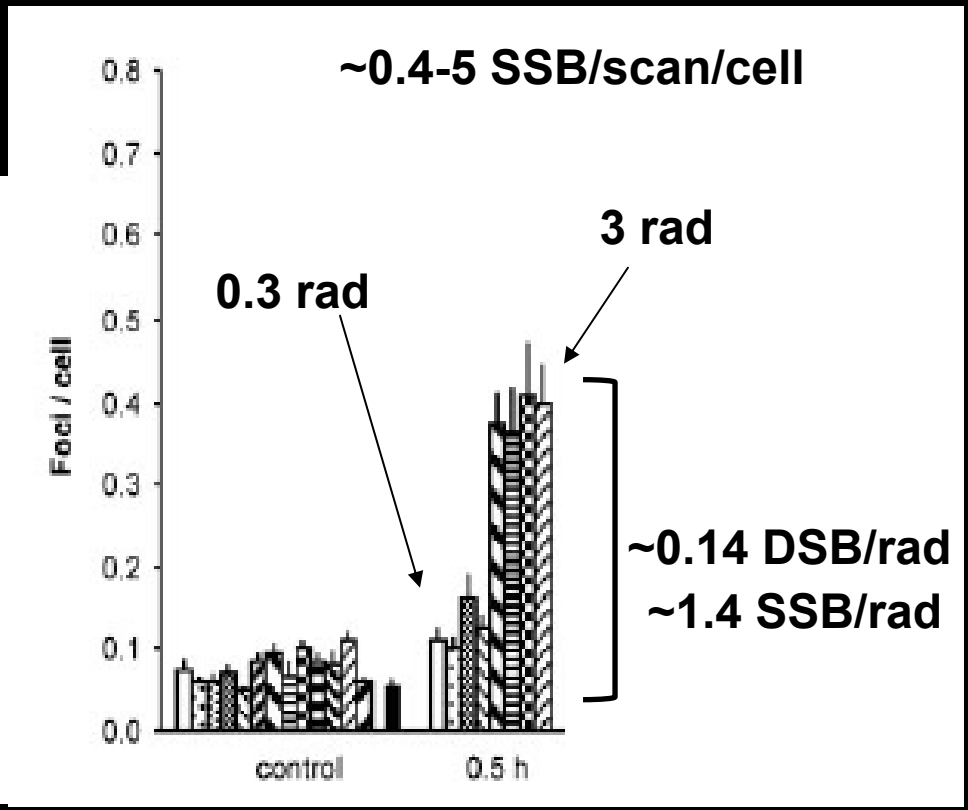
~3.3 SSB/cell

In vivo formation and repair of DNA double-strand breaks after computed tomography examinations

Markus Löbrich*†, Nicole Rief*, Martin Kühne*, Martina Heckmann‡, Jochen Fleckenstein§, Christian Rübe§, and Michael Uder‡¶



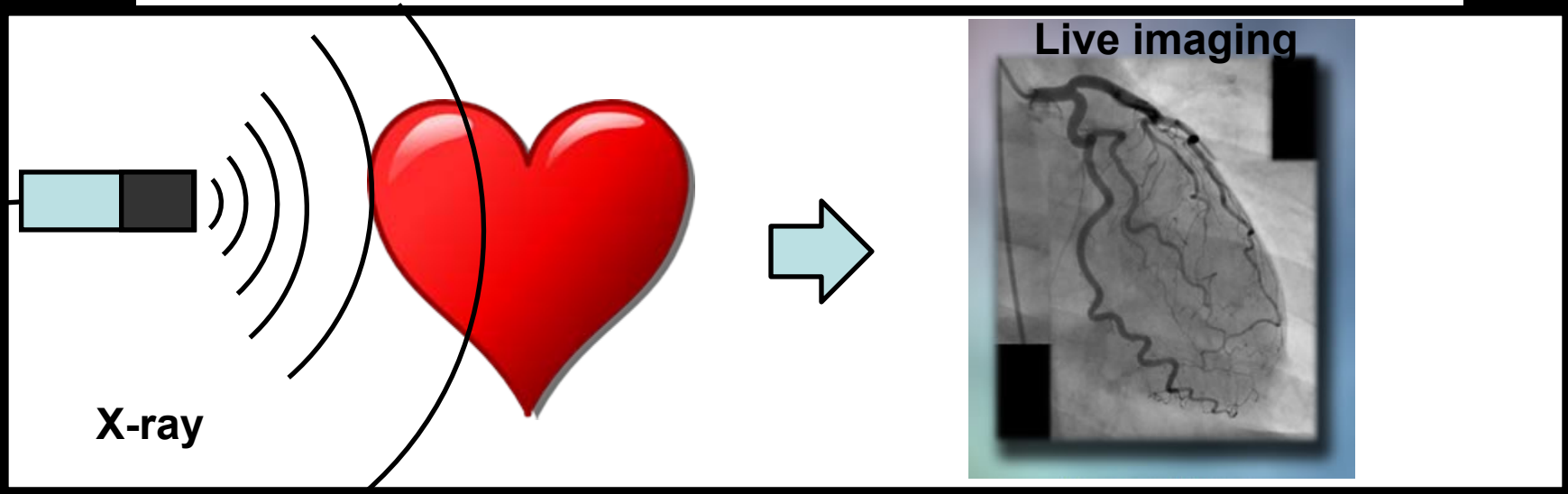


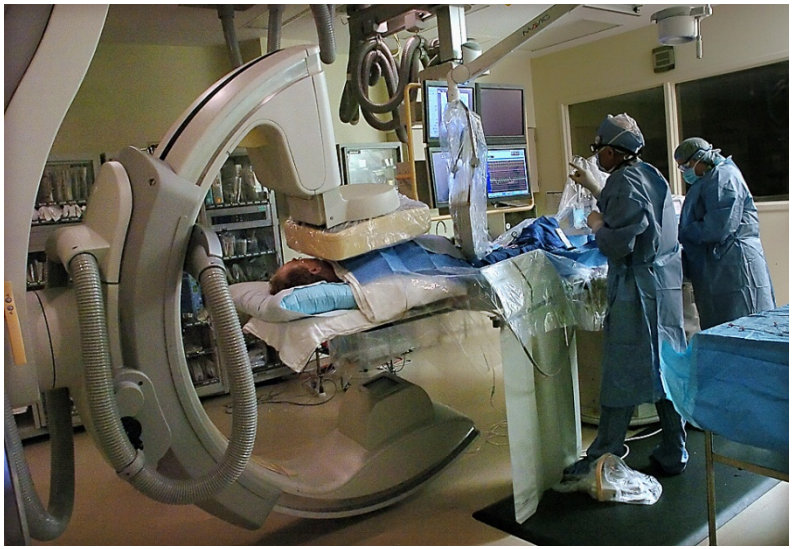


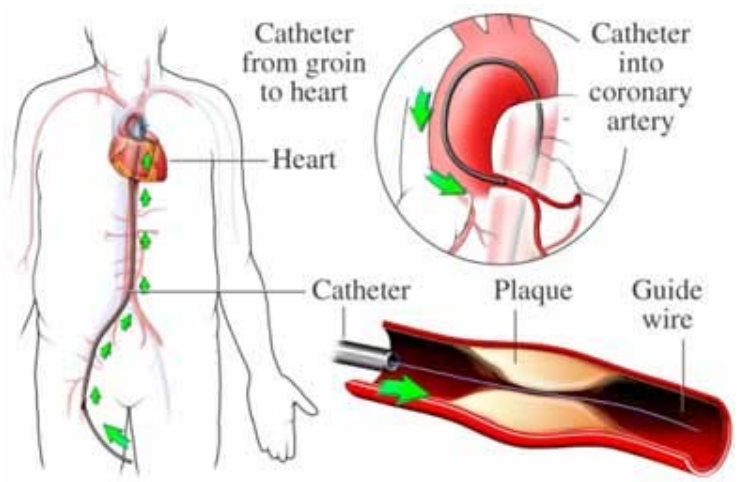
γ-H2AX Foci as a Biomarker for Patient X-Ray Exposure in Pediatric Cardiac Catheterization

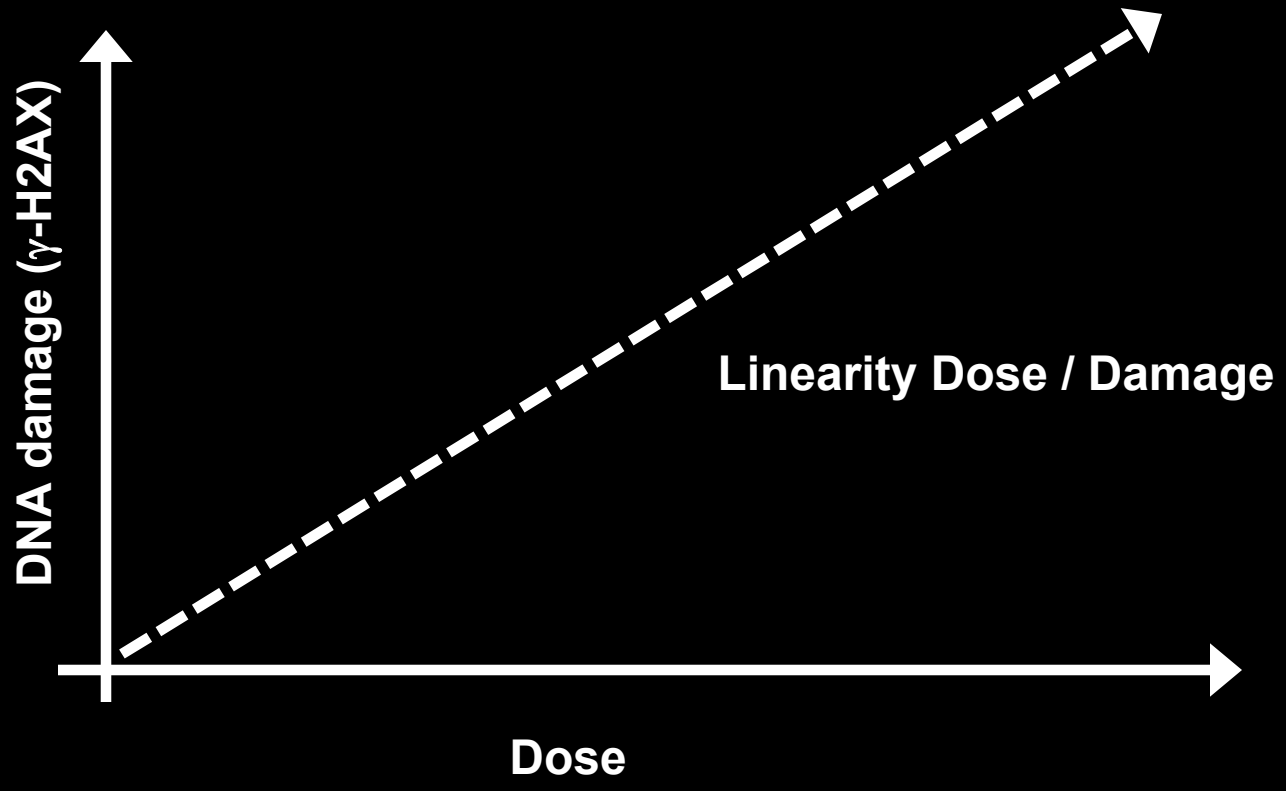
Are We Underestimating Radiation Risks?

Laurence Beels, MSc; Klaus Bacher, PhD; Daniël De Wolf, MD, PhD;
Joke Werbrouck, MSc; Hubert Thierens, PhD







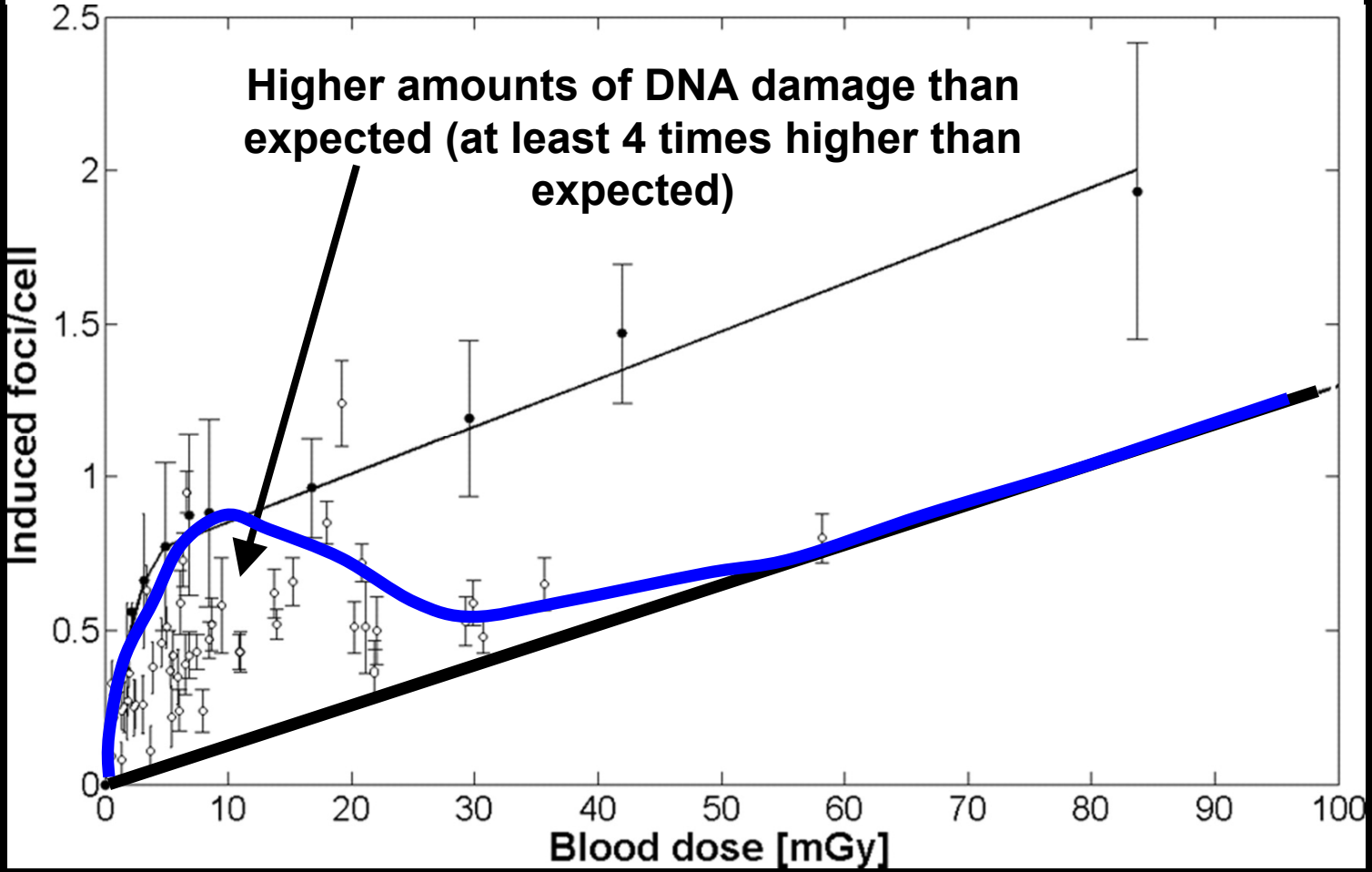

DNA damage (γ-H2AX)
Linearity Dose / Damage
Dose

γ-H2AX Foci as a Biomarker for Patient X-Ray Exposure in Pediatric Cardiac Catheterization

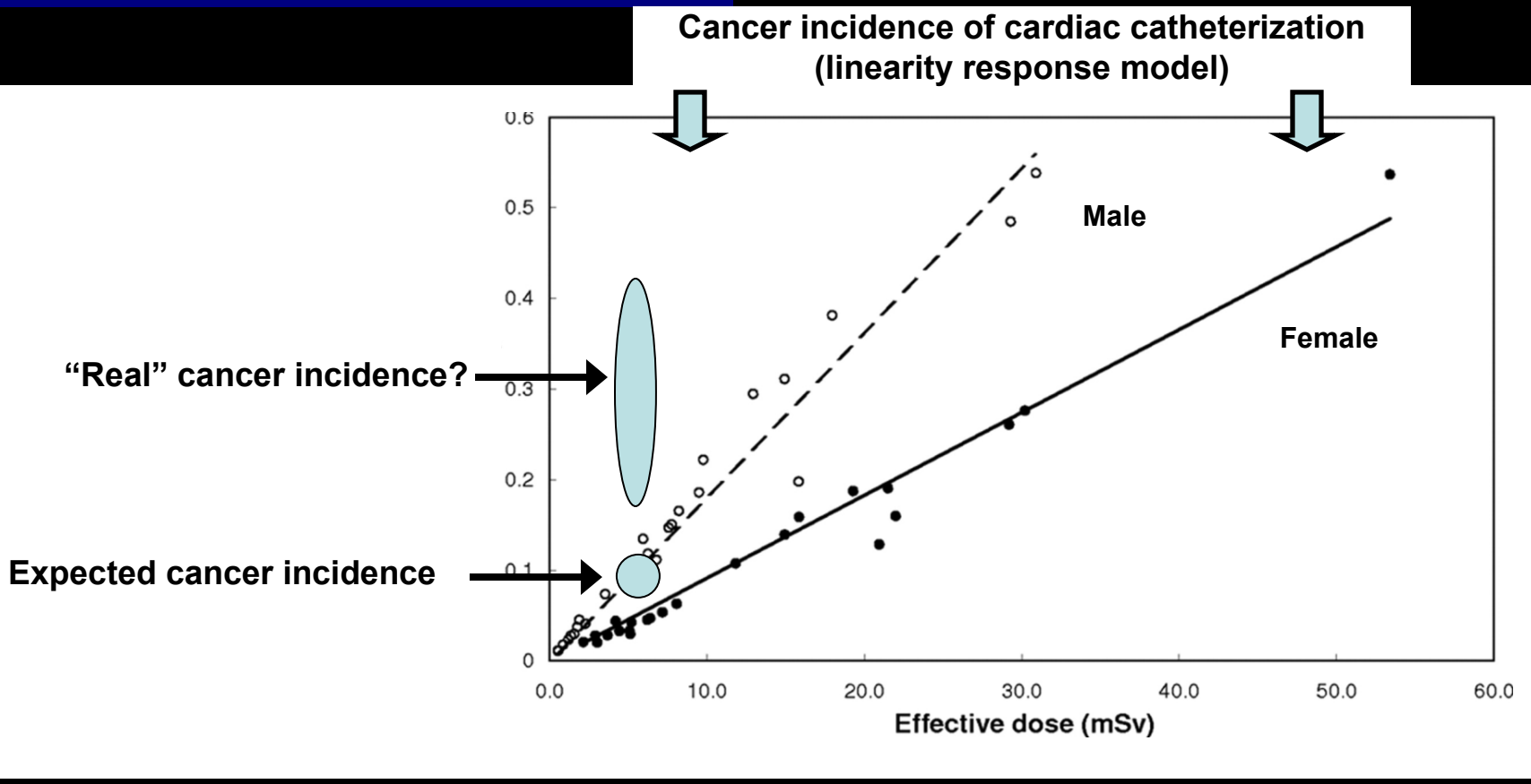
Are We Underestimating Radiation Risks?

49 children
(~ 9 months old)

Laurence Beels, MSc; Klaus Bacher, PhD; Daniël De Wolf, MD, PhD;
Joke Werbrouck, MSc; Hubert Thierens, PhD



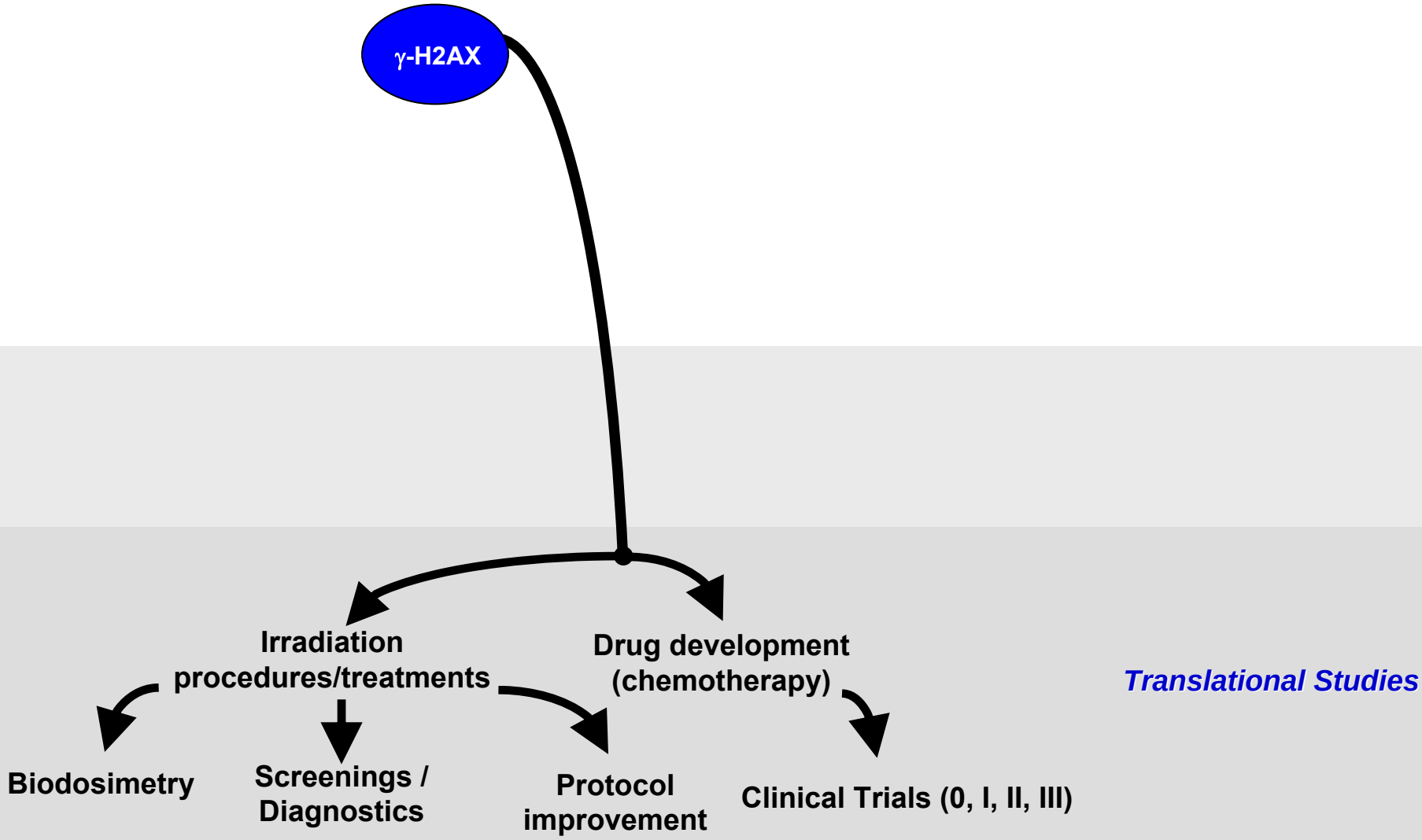
Why it should matter?



Modan B, Keinan L, Blumstein T, Sadetzki S. Cancer following cardiac catheterization in childhood. *Int J Epidemiol*. 2000;29:424–428.

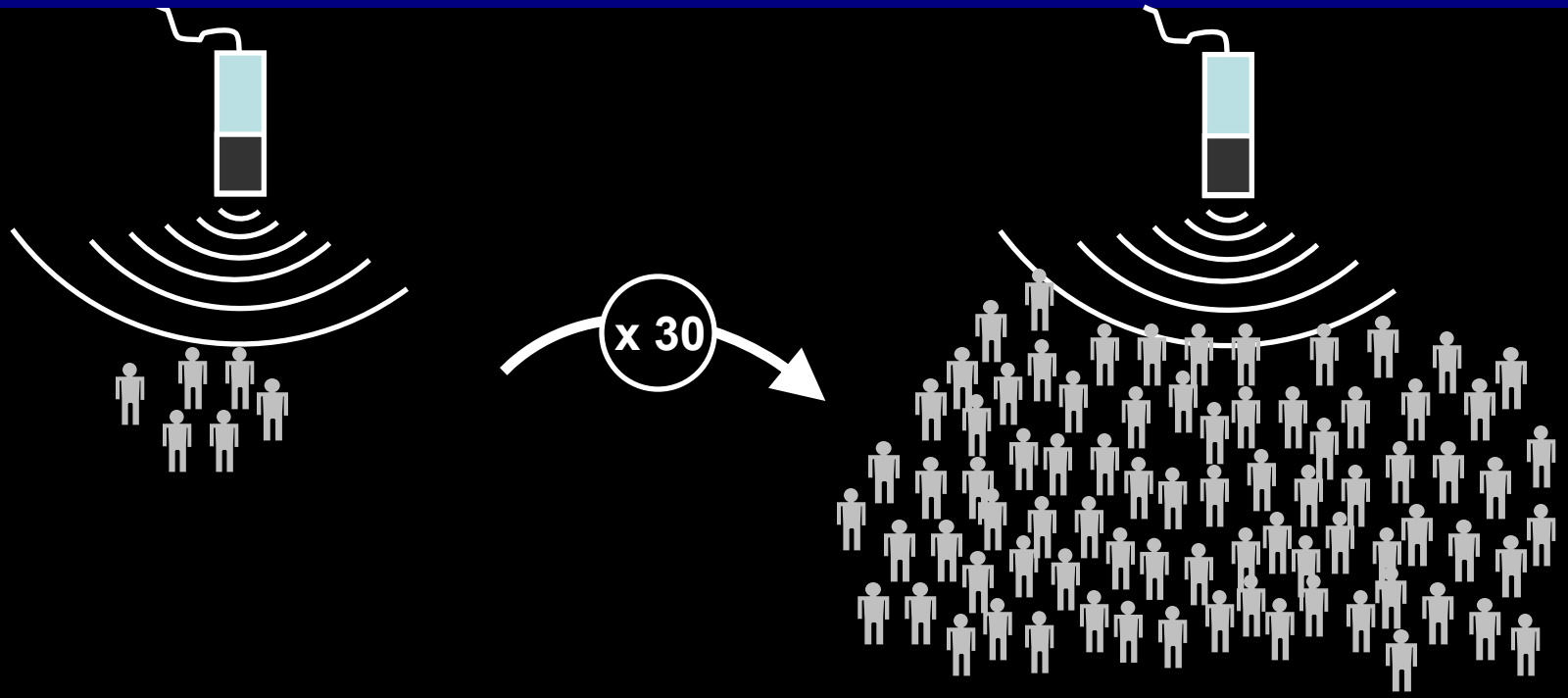
Follow-up of 674 children:
Expected cancer 4.75; observed cancer 11.0 (x2.3)

<u>Conclusion</u>: There is a need for large-scale follow-up studies of populations exposed during childhood to intervention-intensity x-rays



Translational Studies

Why improving protocols ?



► 1980 < 3 millions CT scans

Cancer

► Today > 85 millions CT scans

Cancer

Increased exposure to radiation may lead to new health issues in the near future

Improving protocols

How to reduce radiation exposure in the clinic?

- Less diagnostic radiology ?
- Decrease doses by…

  … improving machines / detection

  … development of drugs limiting the effects of radiation

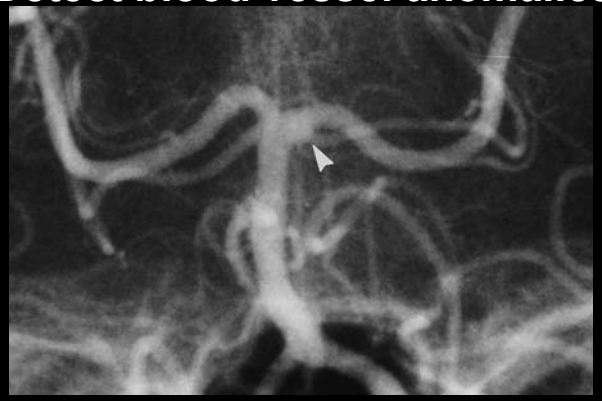
- Can γ-H2AX help? Yes

Comparison of the biological effects of 2 different methods of irradiation for coronary CT angiography

M. A. Kuefner
S. Grudzenski
J. Hamann
S. Achenbach
Michael Lell
K. Anders
S. A. Schwab
L. Häberle
M. Löbrich
M. Uder

Effect of CT scan protocols on x-ray-induced DNA double-strand breaks in blood lymphocytes of patients undergoing coronary CT angiography

Detect blood vessel anomalies



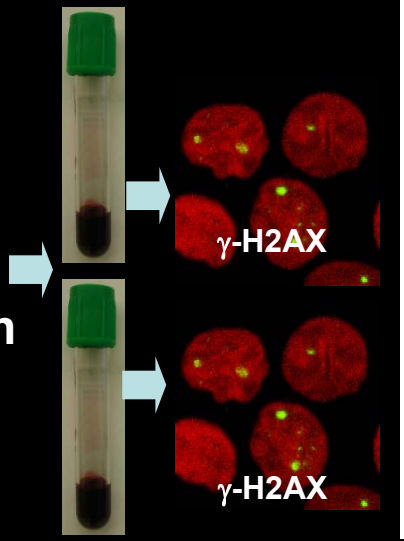
Study aim

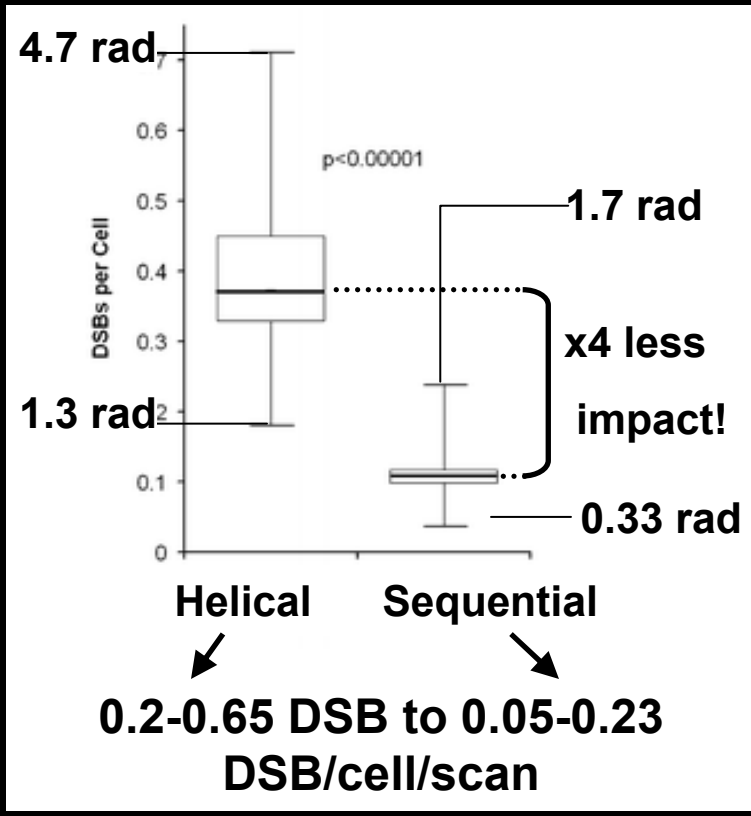
helical data acquisition

or

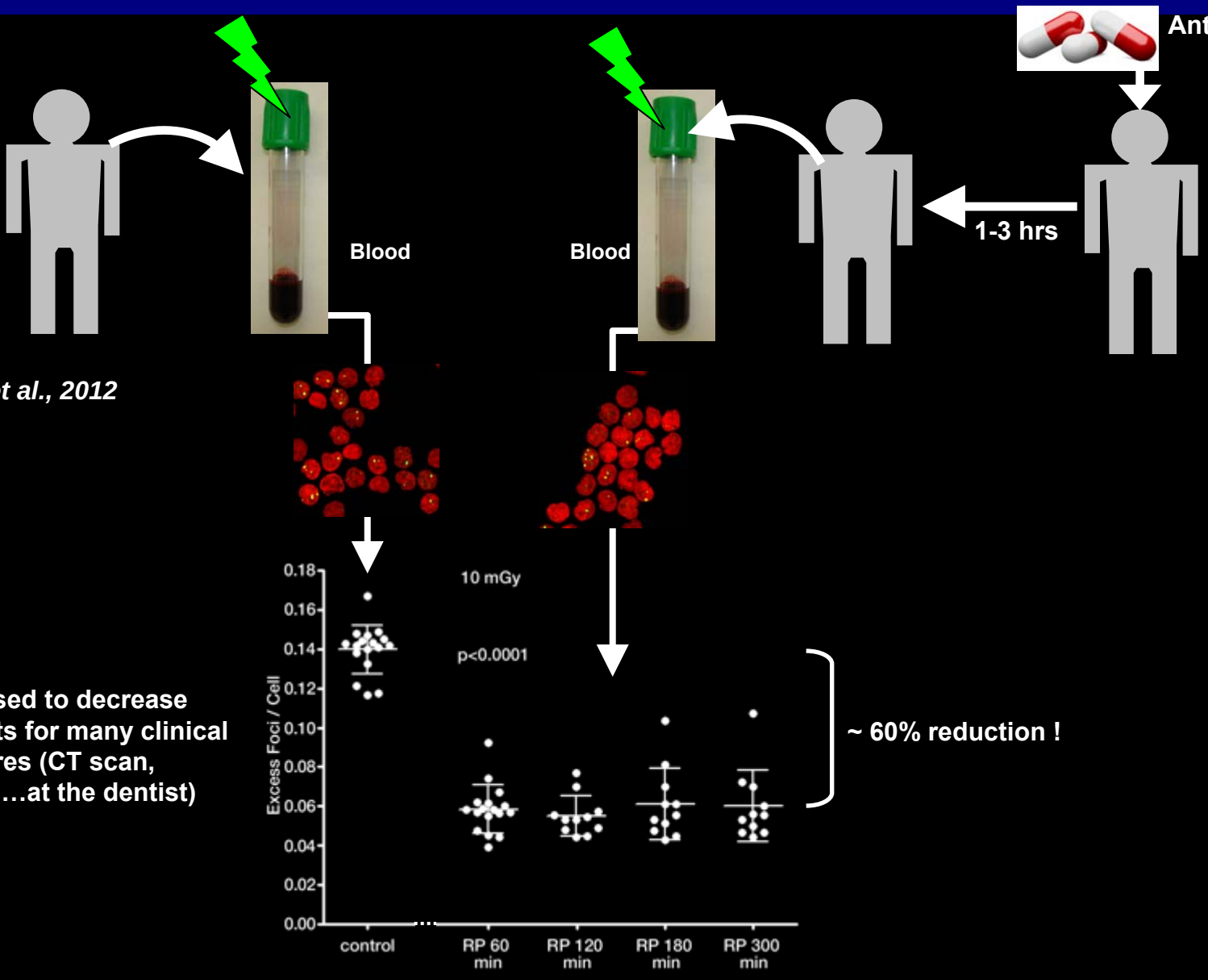
Sequential data acquisition

- know to deliver lower radiation doses
- Less biological effects?

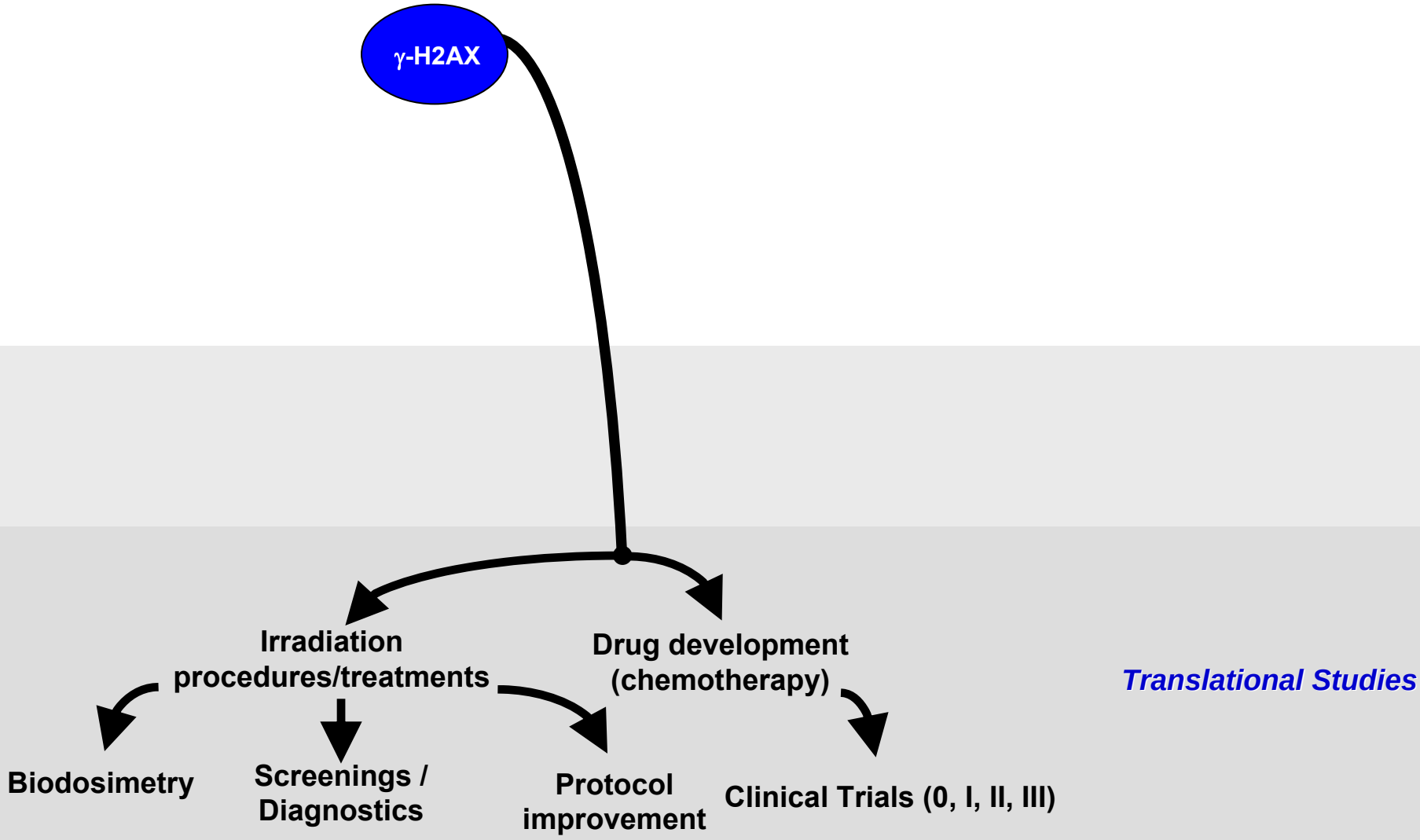




A pill against the effects of clinical radiation (?)



Could be used to decrease radiation effects for many clinical procedures (CT scan, angioplasty,…at the dentist)



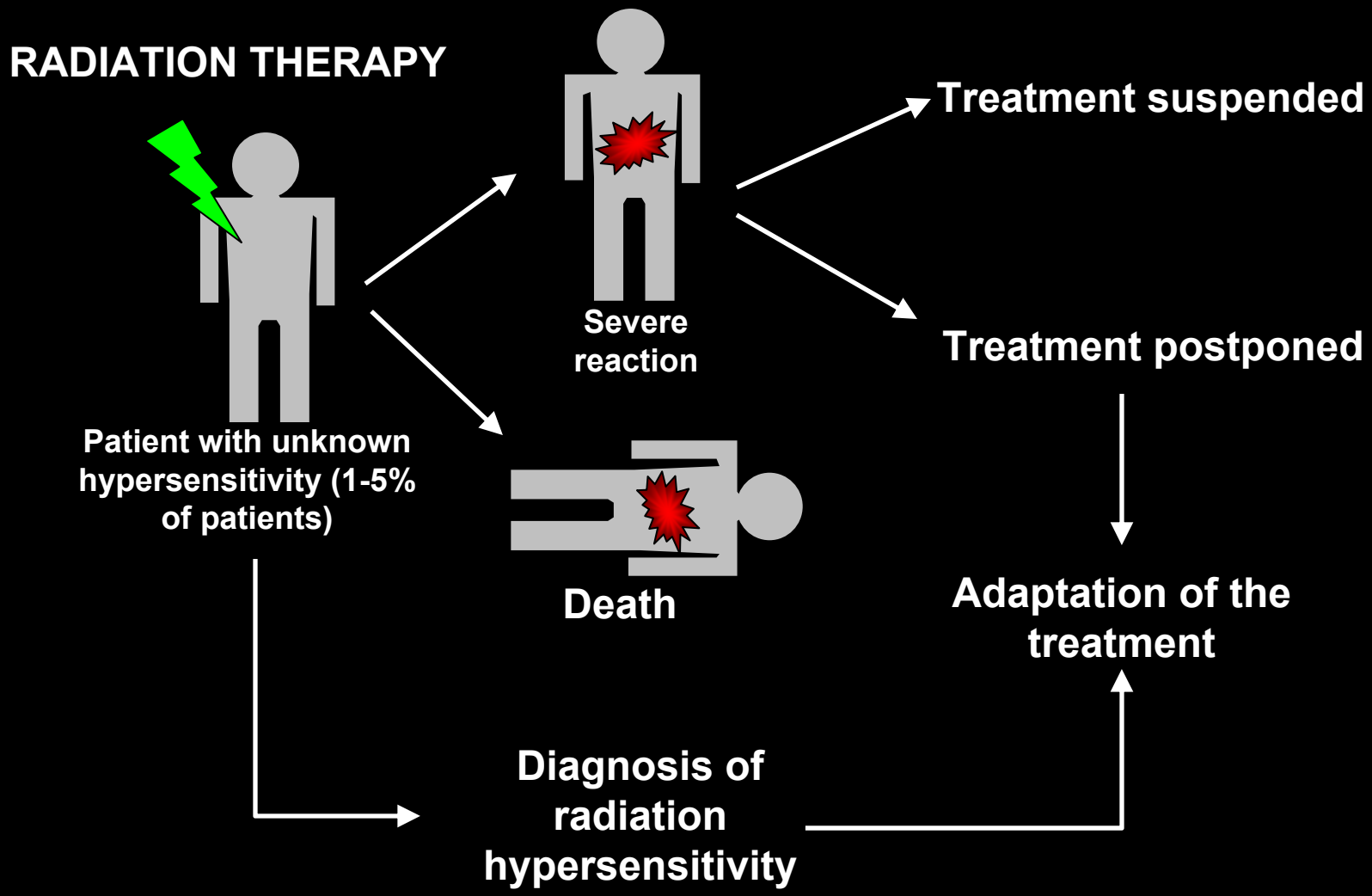
Translational Studies

Table 3
Non-exhaustive list of clinical studies using γ-H2AX for diagnostics.

Samples	Details of diagnostics	IR protocol	Assay	Refs.
Radiation toxicity				
Lymphoblastoid cells	Use of γ-H2AX to discriminate cells from individuals carrying the ATM mutation	0.1 Gy/h–24 h	M	[134]
G0 T cells	T cells from AT and NBS patients show impaired elimination of radiation-induced DSBs	0.5–2 Gy at 2 Gy/min	FC	[135]
Skin fibroblasts	Use of γ-H2AX to show radiation hypersensitivity in cells from parents of RB patients screened as well as in 6 of 15 from apparently normal individuals	0.5–1.0 Gy at 250 cGy/min or 10 cGy/h for 24 h	M	[136]
T-and lymphoblastoid cells/PBMCs	Confirmation of radiosensitive A-T patients	2 Gy	M	[137,138]
PBMCs	Use of γ-H2AX to predict tissue toxicity (mucositis) in patients undergoing head-and-neck radiotherapy	2 Gy (SD) 60–66 Gy (CD)	F	[139]
Skin fibroblasts	Use of γ-H2AX to show that cells from Fanconi anemia patients display a significant delay in the repair of radiation-induced DSBs	1 Gy (0.45 Gy/min)	M	[140]
Fibroblasts	Confirmation of a novel splice variant of the DNA-PKcs gene associated with radiosensitivity	2 Gy	M	[141]
PBMCs	Use of γ-H2AX to identify children at risk for radiation toxicity	1–2 Gy (1 Gy/min)	M	[142]
Lymphoblast cell lines	Identification of a patient with a DNA repair defect during a screening for radiosensitivity	1, 2, 4 Gy (0.62 Gy/min)	M	[86]
PBMCs	Use of γ-H2AX to predict excessive normal tissue toxicity in radiotherapy patients	2 Gy	F	[88]
Blood samples	γ-H2AX as a molecular predictor of prostate cancer radiosensitivity	N/A	N/A	NCT00523471 (#)
Other diagnosis				
Samples	Details of diagnostics		Assay	Refs.
Tumor biopsies	γ-H2AX as a potential cancer biomarker		M	[90]
Tumor biopsies	Diagnosis for metastatic renal cell carcinoma		M	[92,143]
Colon biopsies	Increased DNA damage in colon of ulcerative colitis patients		M	[99]
Melanomas	Evaluation of the γ-H2AX assay as a marker for melanocytic lesions		M	[91]
Bladder urothelial carcinoma	Use of γ-H2AX to predict cancer recurrence and/or progression		M	[144]
PBMCs	Increased DNA damage and cell death in lymphocytes from patients with occult HBV infections		N/A	[104]
Immortalized lymphoblasts	Increased basal DNA damage in cells from individuals with schizophrenia		F	[106]
Lung tissue (alveolar wall cells)	Increased DNA damage levels in lungs of advanced COPD patients		M	[100]
Malignant plasma cells	DNA damage escalation during the development of multiple myeloma		M	[95]
Fibroblasts, T cells	Increased γ-H2AX in lymphocytes and fibroblasts of dyskeratosis congenital patients		M,F	[102]
PBMCs	Increased DNA damage in lymphocytes from obese and overweight children		M	[101]
Curettage specimens of endometrial cancer	Use of γ-H2AX as an additional histopathological prognostic parameter in patients with endometrial cancer		M	[145]
Squamous epithelia of the uterine cervix	Use of γ-H2AX as a cancer biomarker in patients with cervix cancer		M	[146]
N/A	Use of γ-H2AX as a biomarker in women undergoing IVF Treatment		N/A	NCT00685282 (#)

Abbreviations: M: microscopy (immunocytochemistry or immunohistochemistry); F: flow cytometry; N/A: not applicable; PBMCs, peripheral blood mononuclear cells; SD, single dose; CD, cumulated doses; (#): ClinicalTrials.gov identifier.

Most common use for diagnostic = radiation hypersensitivity



DEFICIENCY in DSB REPAIR

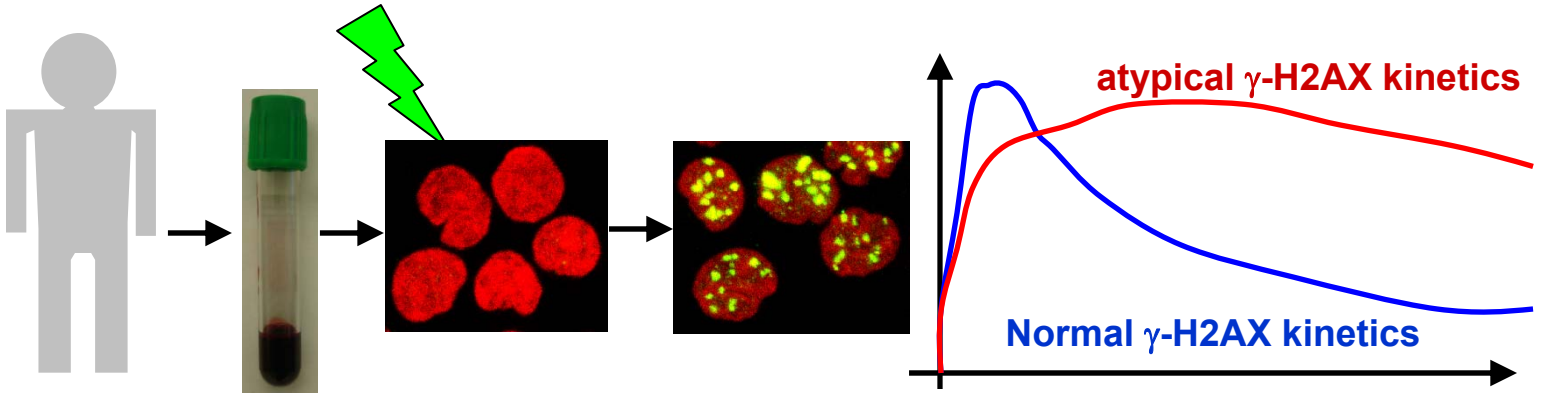
↓

Alteration in γ-H2AX kinetics

↓

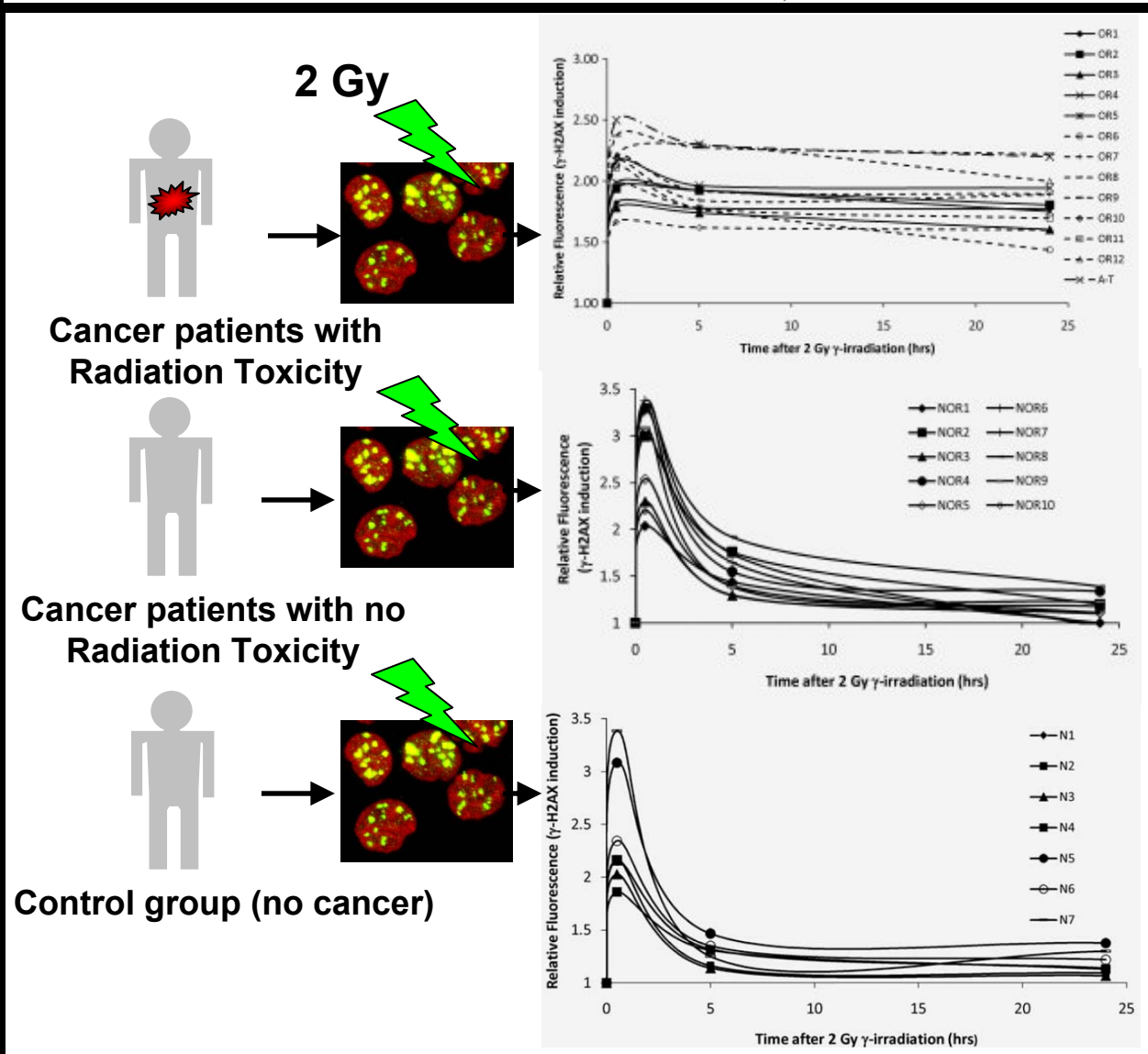
RADIATION HYPERSENSITIVITY

Diagnostic scheme



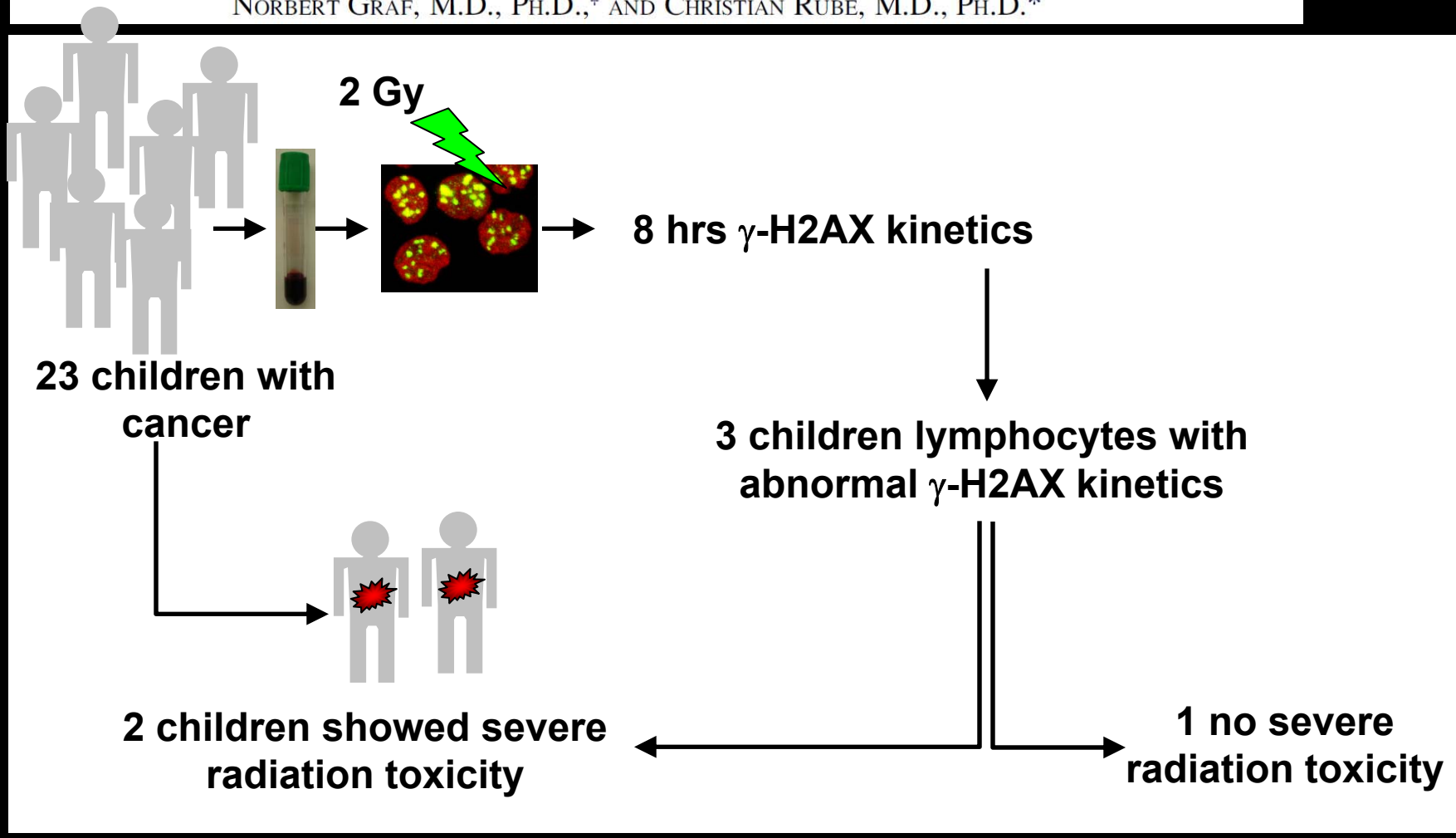
Prolonged expression of the γ-H2AX DNA repair biomarker correlates with excess acute and chronic toxicity from radiotherapy treatment

Emma C. Bourton[1], Piers N. Plowman[2], Daniel Smith[2], Colin F. Arlett[3] and Christopher N. Parris[1]



DNA REPAIR ALTERATIONS IN CHILDREN WITH PEDIATRIC MALIGNANCIES: NOVEL OPPORTUNITIES TO IDENTIFY PATIENTS AT RISK FOR HIGH-GRADE TOXICITIES

CLAUDIA E. RÜBE, M.D., PH.D.,* ANDREAS FRICKE, PH.D.,* RUTH SCHNEIDER, M.D.,* KARIN SIMON, M.D.,* MARTIN KÜHNE, PH.D.,* JOCHEN FLECKENSTEIN, M.D.,* STEFAN GRÄBER, PH.D.,† NORBERT GRAF, M.D., PH.D.,‡ AND CHRISTIAN RÜBE, M.D., PH.D.*

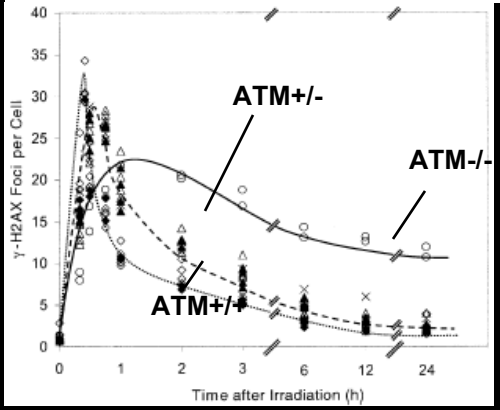


Radiation hypersensitivity – Identify individual with DNA repair-deficiency disorder

Levels of γ-H2AX Foci after Low-Dose-Rate Irradiation Reveal a DNA DSB Rejoining Defect in Cells from Human *ATM* Heterozygotes in Two AT Families and in Another Apparently Normal Individual

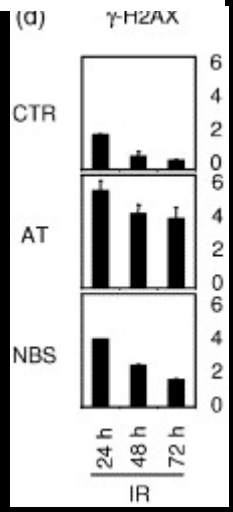
Takamitsu A. Kato,[a] Hatsumi Nagasawa,[a] Michael M. Weil,[a] J. B. Little[b] and J. S. Bedford[a,1]

[a] *Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, Colorado 80523; and* [b] *Center for Radiation Sciences and Environmental Health, Harvard School of Public Health, Boston, Massachusetts 02115*



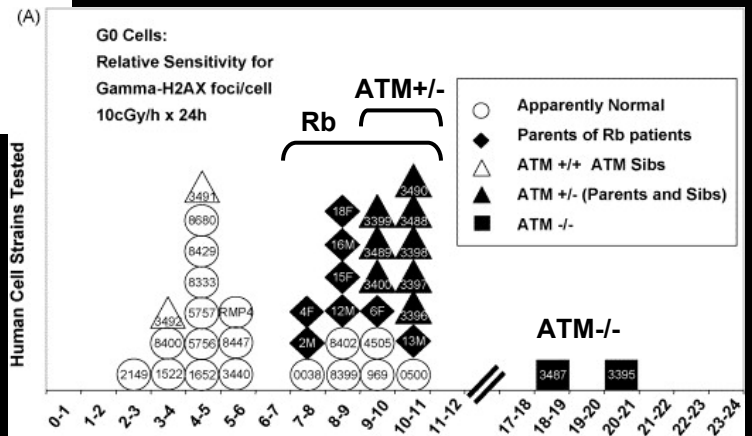
Impaired elimination of DNA double-strand break-containing lymphocytes in ataxia telangiectasia and Nijmegen breakage syndrome

Paola Porcedda[a,1], Valentina Turinetto[a,1], Erica Lantelme[a], Enrico Fontanella[b], Krystyna Chrzanowska[c], Riccardo Ragona[d], Mario De Marchi[a], Domenico Delia[b], Claudia Giachino[a,]*

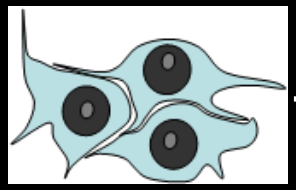


A defect in DNA double strand break processing in cells from unaffected parents of retinoblastoma patients and other apparently normal humans

Takamitsu A. Kato[a], Paul F. Wilson[a,d], Hatsumi Nagasawa[a], Markus M. Fitzek[b], Michael M. Weil[a], John B. Little[c], Joel S. Bedford[a,]*



Cancer biomarker



CANCER CELLS → Increased Genomic Instability → Increased DNA DAMAGE → High Levels of γ-H2AX

Brief Report

γH2AX in Cancer Cells

A Potential Biomarker for Cancer Diagnostics, Prediction and Recurrence

Olga A. Sedelnikova*
William M. Bonner

Utility of Antiphosphorylated H2AX Antibody (γ-H2AX) in Diagnosing Metastatic Renal Cell Carcinoma

Matthew J. Wasco, MD and Robert T. Pu, MD, PhD

Expression of γ-H2AX in endometrial carcinomas: An immunohistochemical study with p53

Andreas H. Brunner [a,*], Susanne Hinterholzer [a], Paul Riss [a], Georg Heinze [b], Katharina Weiss [b], Hermann Brustmann [c]

[a] Department of Obstetrics and Gynecology, Landesklinikum Thermenregion Moedling/Vienna, Moedling/Vienna, Austria
[b] Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria
[c] Department of Pathology, Landesklinikum Thermenregion Moedling/Vienna, Moedling/Vienna, Austria

Comparison of PAX-2, RCC Antigen, and Antiphosphorylated H2AX Antibody (γ-H2AX) in Diagnosing Metastatic Renal Cell Carcinoma by Fine-Needle Aspiration

Matthew J. Wasco, M.D.[1*] and Robert T. Pu, M.D., Ph.D.

Original Article

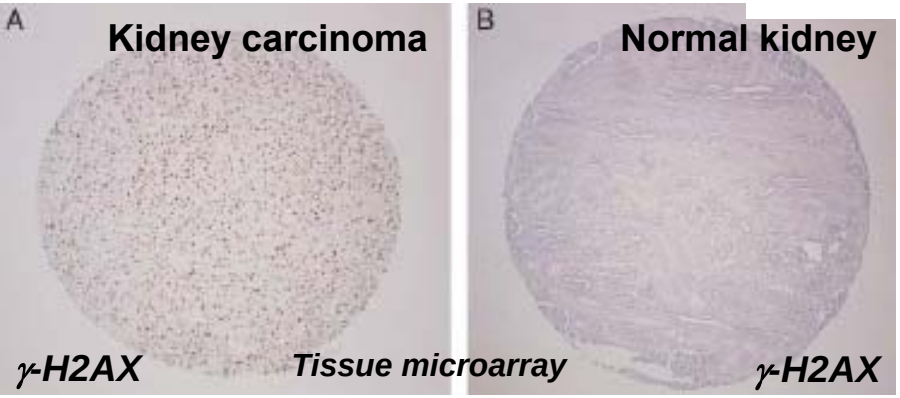
Expression of Phosphorylated Histone H2AX (γ-H2AX) in Normal and Neoplastic Squamous Epithelia of the Uterine Cervix: An Immunohistochemical Study With Epidermal Growth Factor Receptor

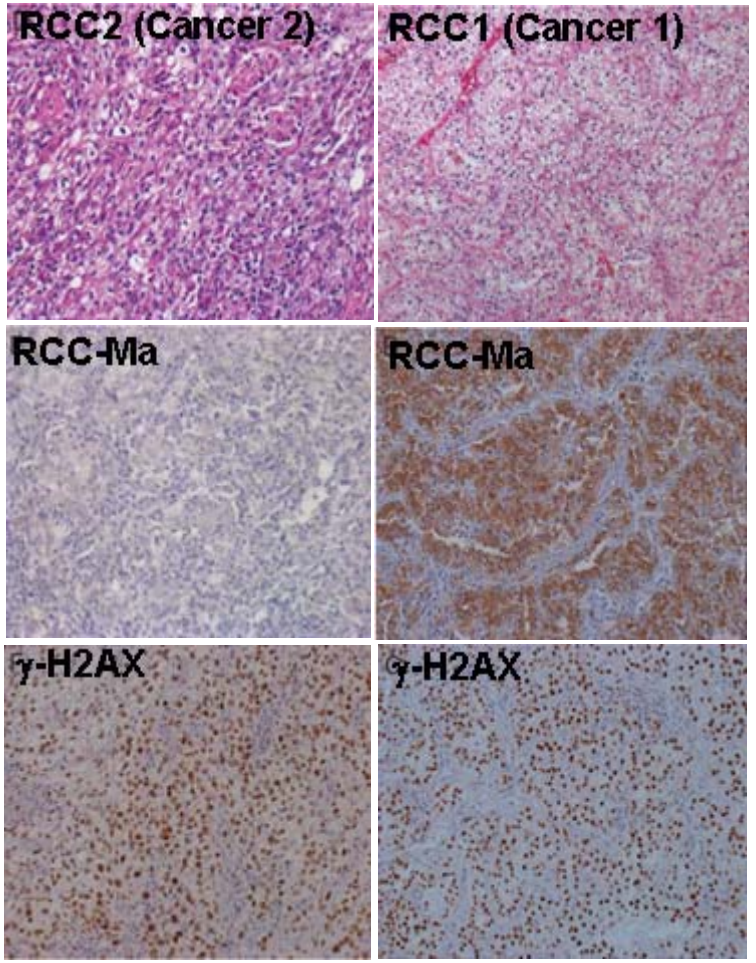
Hermann Brustmann, M.D., Ph.D., Susanne Hinterholzer, M.D., and Andreas Brunner, M.D.

Cancer biomarker

Utility of Antiphosphorylated H2AX Antibody (γ-H2AX) in Diagnosing Metastatic Renal Cell Carcinoma

Matthew J. Wasco, MD and Robert T. Pu, MD, PhD





► **Renal Cell Carcinoma can be challenging to diagnose**

► **A marker, RCC-Ma is used, for RCC diagnosis**

However, not all Renal Cell Carcinoma are RCC-Ma positive (25-32% RCC-Ma negative)

Staining can be week in small biopsies samples, can react with normal tissues or stain other cancers

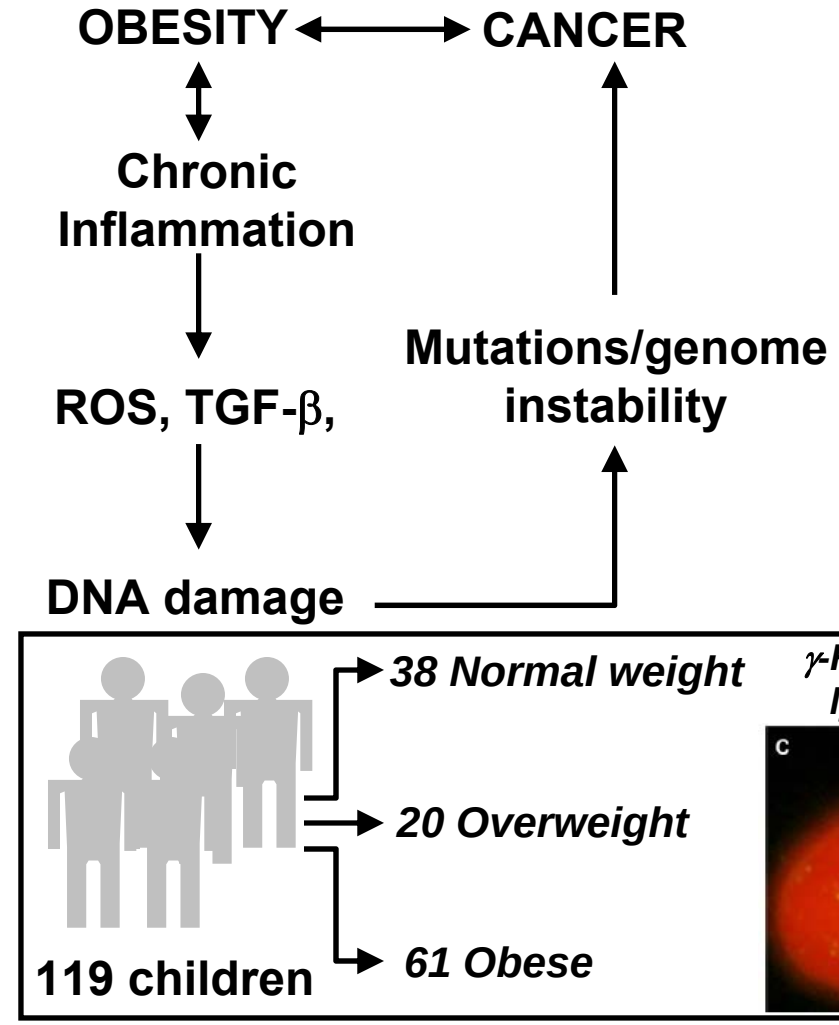
"In fact, γH2AX stained 9/9 tumors (…) whereas RCC-Ma only stained 4/9 cases. Five cases of grade 4 RCC were not stained by RCC-Ma but all of them were positive for γ-H2AX

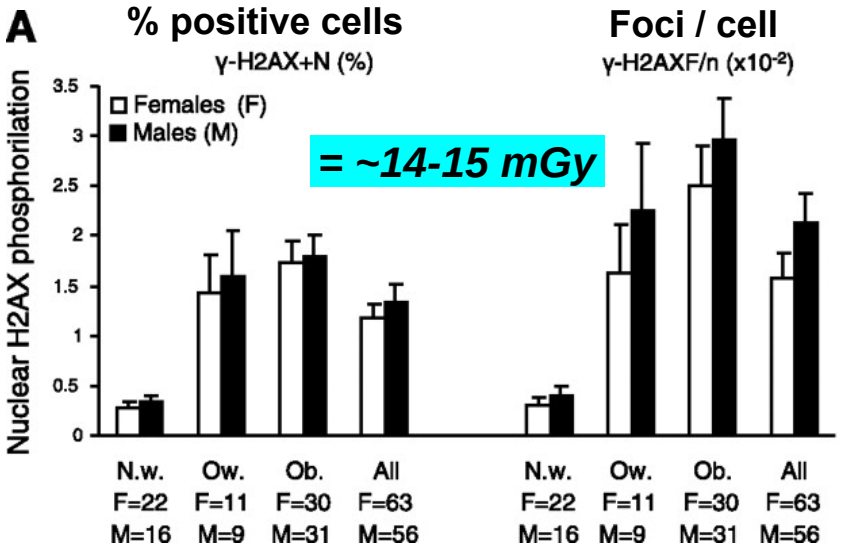
Other diagnostics (chronic inflammation and cancer risk)

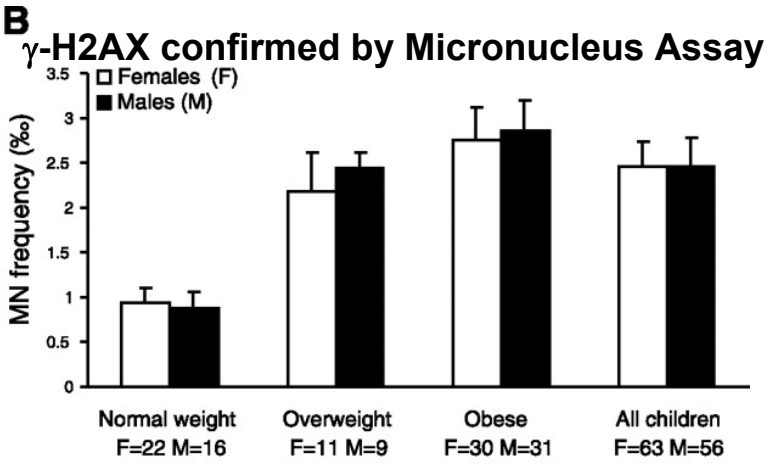
Nuclear damage in peripheral lymphocytes of obese and overweight Italian children as evaluated by the γ-H2AX focus assay and micronucleus test

Roberto Scarpato,*[,1] Carmela Verola,* Barbara Fabiani,* Vanessa Bianchi,[†] Giuseppe Saggese,[†] and Giovanni Federico[†]

*Dipartimento di Biologia, Unità di Genetica, Mutagenesi ed Epidemiologia Ambientale, University of Pisa, Pisa, Italy; and [†]Sezione di Endocrinologia e Diabetologia Pediatrica, Dipartimento Materno-Infantile, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy







Other diagnostics (chronic inflammation and cancer risk)

Ulcerative colitis is a disease of accelerated colon aging: evidence from telomere attrition and DNA damage

Rosa Ana Risques[1], Lisa A. Lai[2], Teresa A. Brentnall[2], Lin Li[3], Ziding Feng[3], Jasmine Gallaher[1], Margaret T. Mandelson[3,4], John D. Potter[3], Mary P. Bronner[5], and Peter S. Rabinovitch[1,3]

1*Department of Pathology, University of Washington, Seattle, WA*

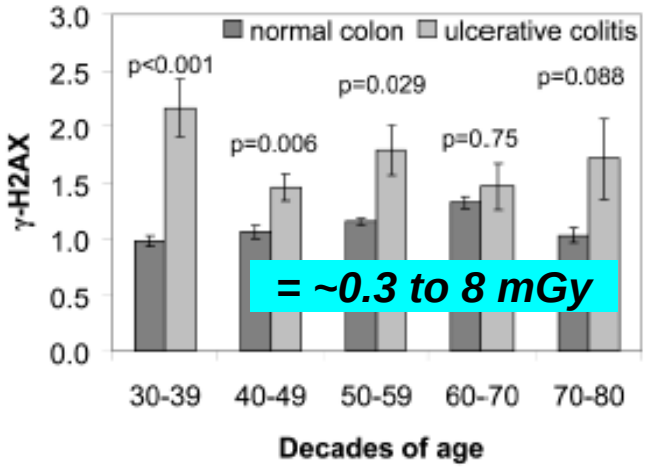
2*Department of Medicine and Division of Gastroenterology, University of Washington, Seattle, WA*

3*Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA*

4*Center for Health Studies, Group Health Cooperative, Seattle, WA*

5*Department of Anatomic Pathology, Cleveland Clinic, Cleveland, OH.*

Ulcerative colitis (predisposes to colorectal cancer)

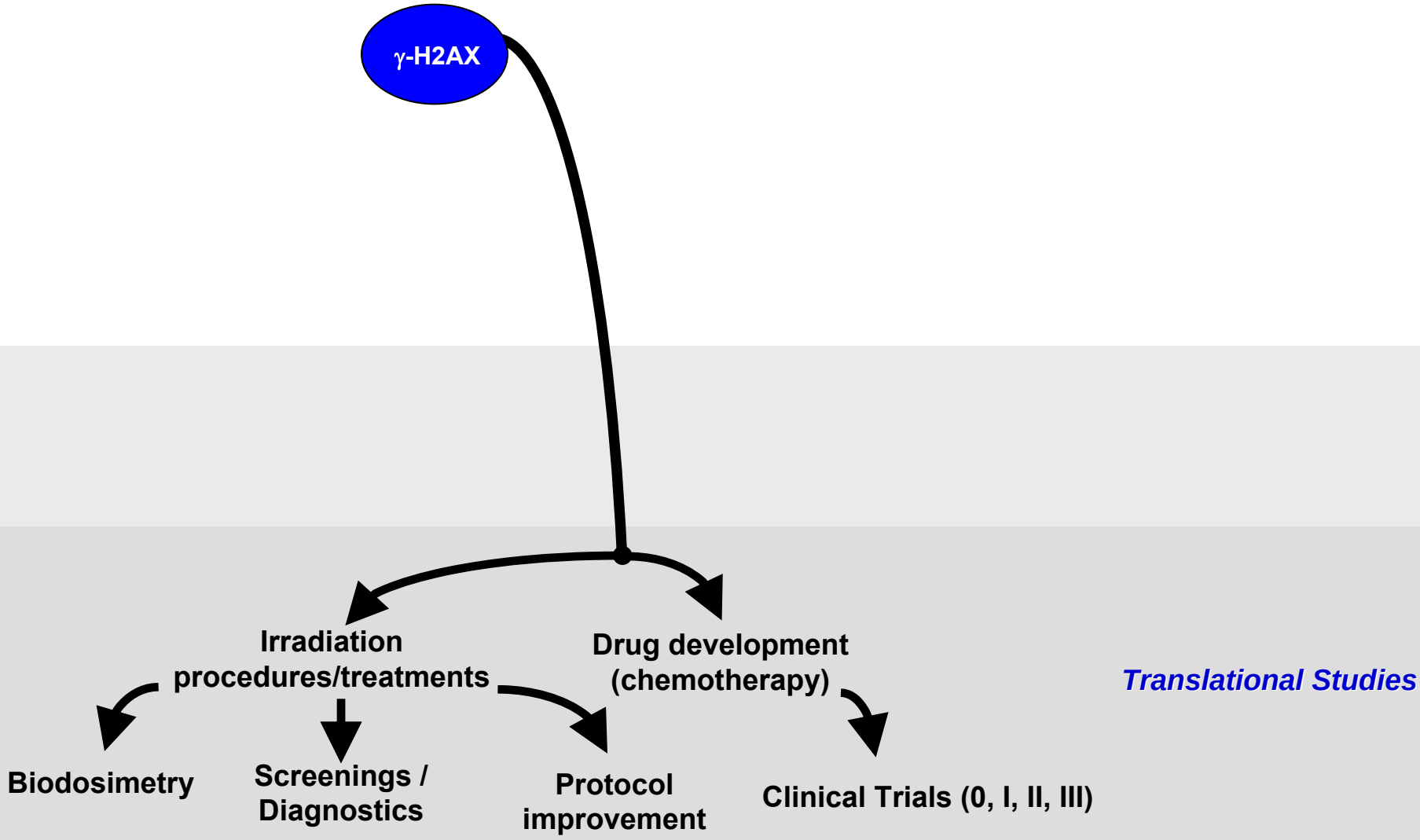


Oxidative DNA damage in lung tissue from patients with COPD is clustered in functionally significant sequences

Viktor M Pastukh[1]
Li Zhang[2]
Mykhaylo V Ruchko[1]
Olena Gorodnya[1]
Gina C Bardwell[1]
Rubin M Tuder[2]
Mark N Gillespie[1]

[1]Department of Pharmacology and Center for Lung Biology, University of South Alabama College of Medicine, Mobile, AL, USA; [2]Program in Translational Lung Research, Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado at Denver, Aurora, CO, USA

Lung cancer incidence increased in individuals with COPD **(Chronic Obstructive Pulmonary Disease)**



Translational Studies

Table 2
Non-exhaustive list of clinical studies using the γ-H2AX assay to measure chemotherapeutic drug effects in cancer patients.

Condition	Drug(s)	Tissues analyzed	γ-H2AX detection	Phase	References or ClinicalTrials.gov identifier
Head and neck squamous cell carcinoma	Cisplatin/Raltegravir (MK-0518)	Tumor	M	0	NCT01275183
Solid tumors	Veliparib (ABT-888)/irinotecan	Tumor/PBMCs	M	I	[129]
Her-2 negative metastatic breast cancer	Veliparib/Carboplatin	CTCs	M?	I	[130]
Solid tumors and lymphomas	Veliparib/Topotecan	CTCs/PBMCs	M	I	[84]
Breast cancer	Olaparib (AZD2281)	Eyebrows	M	I	[49]
MDS, CML, leukemia, and AML	5-Azacytidine/Entinostat (MS-275)	PBMCs	I	I	[131]
AML	Tipifarnib/Etoposide	AML marrow blasts	F	I	[132]
Solid tumors	SJG-136	PBMCs/Tumor	IHC	I	[133]
Leukemias	Clofarabine/Cyclophosphamide	PBMCs	F	I	[82]
MDS, AML, CML	5-Azacytidine/Entinostat	N/A	N/A	I (*)	NCT00101179
Metastatic, unresectable or recurrent solid tumors	Veliparib/mitomycin C	Blood (PBMCs)	M	I	NCT01017640
Solid tumors; BRCA1, BRCA2 mutations carriers		MCs/skin/hairs	N/A	I	NCT00892736
Solid tumors or lymphomas		ood (PBMCs)/tumor	M	I	NCT00810966
Advanced solid tumors	Iniparib (BSI-201)	N/A	N/A	I (*)	NCT01161836
Solid malignancies	7-t-butyldimethylsilyl-10-hydroxycamptothecin	Tumor	M/I	I	NCT01202370
Lymphoma, solid tumors	Indenoisoquinolines	Tumor/Skin	N/A	I	NCT01245192
Glioblastoma		Tumor	M	I	NCT01390571
Glioblastoma		N/A	N/A	I, II	NCT00687765
Uterine carcinosarcoma		N/A	N/A	II	NCT00687687
Triple negative breast cancer		N/A	N/A	II	NCT00813956
Ovarian cancer	Iniparib	N/A	N/A	II	NCT01033123
Glioma	TH-302	N/A	M/I	II	NCT01403610
Breast cancer	Gemcitabine/carboplatin/Iniparib	N/A	N/A	III	NCT00938652
Stage IV squamous non-small-cell lung cancer	Gemcitabine/Carboplatin with or without Iniparib	N/A	N/A	III	NCT01082549

Abbreviations: M, microscopy (immunocytochemistry or immunohistochemistry); I, immunoblotting; F, flow cytometry; CTCs, circulating tumor cells; PBMCs, peripheral blood mononuclear cells; N/A, not specified; (*) study completed; CML, chronic myelogenous leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

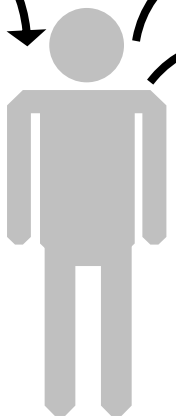
► Many types of cancer

► Many types of drugs

Examples of Studies at NIH

1. DNA alkylating agent
2. Drug combination

Drug(s)



Blood samples → γ-H2AX

Hair samples → γ-H2AX

Abstract #94874

Phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of intravenous dimethane sulfonate (DMS612, NSC 281612) in advanced malignancies.

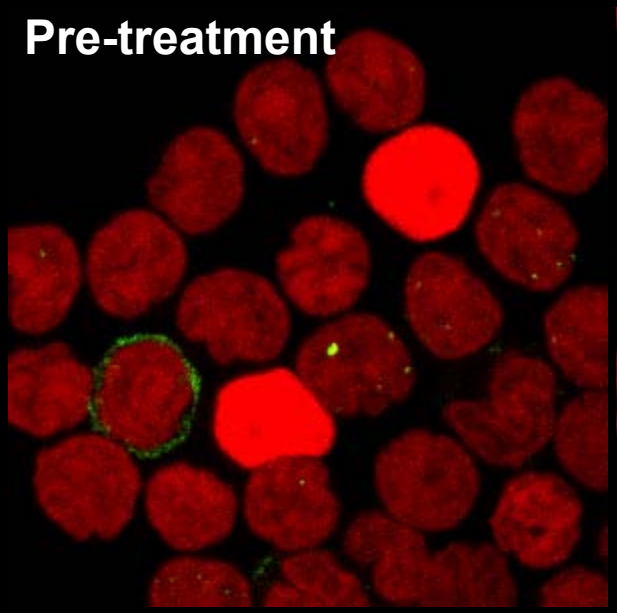
Susan Elaine Bates, Sanjeeve Balasubramaniam, Robert A Parise, Christina Bryla, William Bonner, Christophe E. Redon, Asako Nakamura, John Joseph Wright, Richard Piekarz, Yixing Jiang, Julie Eiseman, Edward Chu, Chandra Prakash Belani, Jan Hendrik Beumer, Leonard Joseph Appleman

ASCO-Abstract #98190

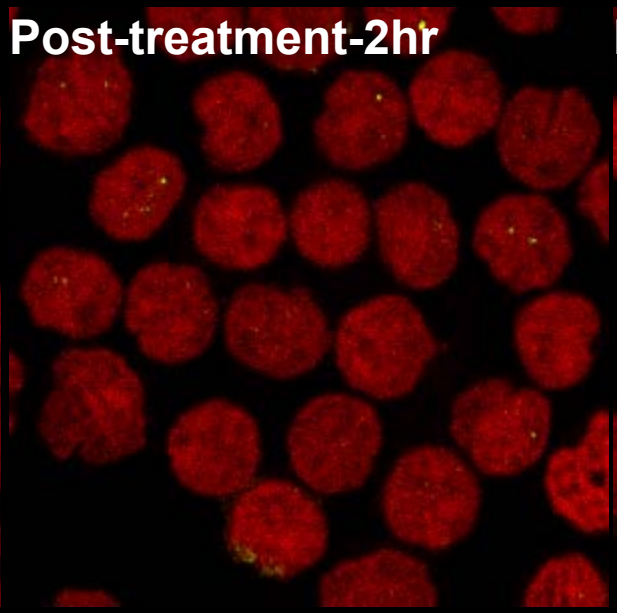
Proof of mechanism (POM) in the first-in-human trial of two novel indenoisoquinoline, non-camptothecin topoisomerase I (TOP1) inhibitors.

James H. Doroshow, Jiuping Jay Ji, Alice Chen, Deborah Allen, Yiping Zhang, Scott M Lawrence, Thomas D. Pfister, Lihua Wang, Christophe E. Redon, William Bonner, Giovanna Speranza, Marcie K. Weil, Julie Eiseman, Julianne L. Holleran, Robert J. Kinders, Jan Hendrik Beumer, Ralph E. Parchment, Yves Pommier, Joseph E. Tomaszewski, Shivaani Kummar

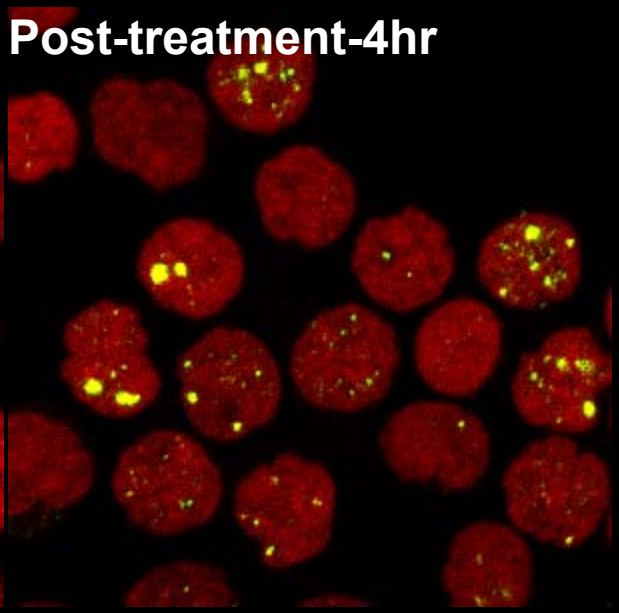
Pre-treatment



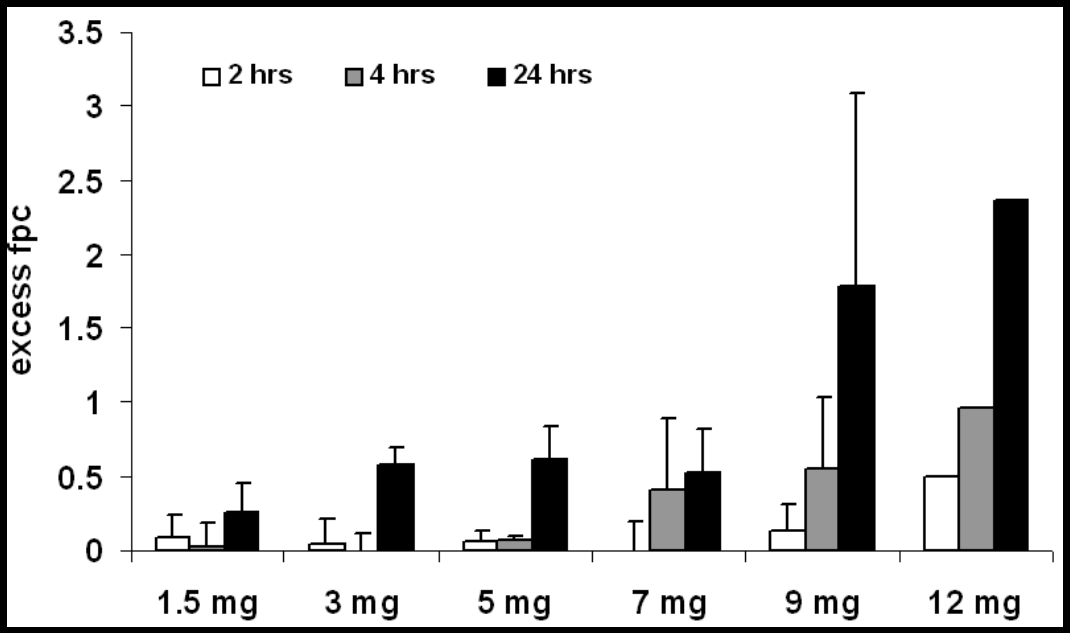
Post-treatment-2hr



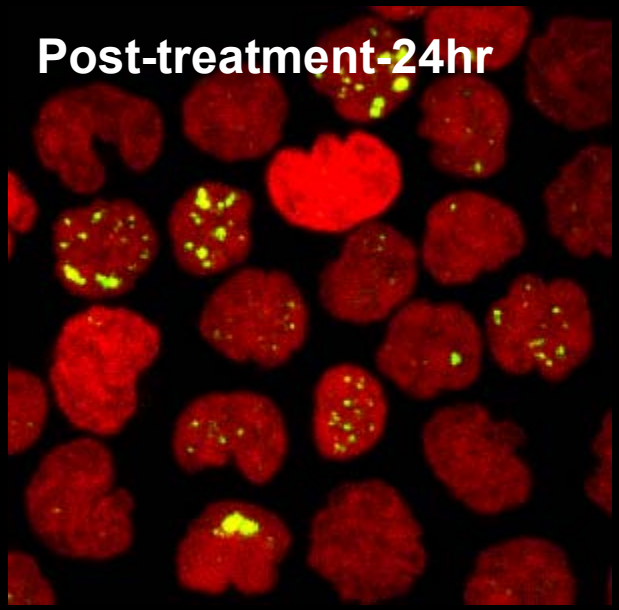
Post-treatment-4hr

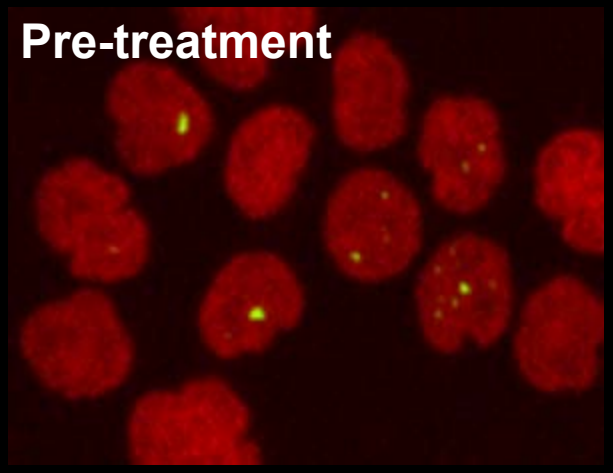


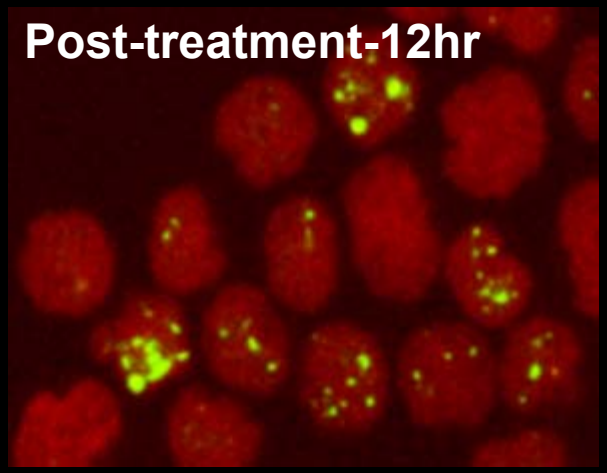
Lymphocytes - DNA alkylating agent

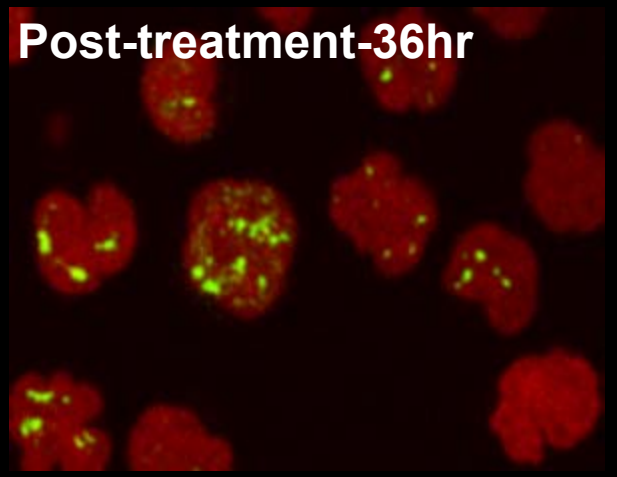


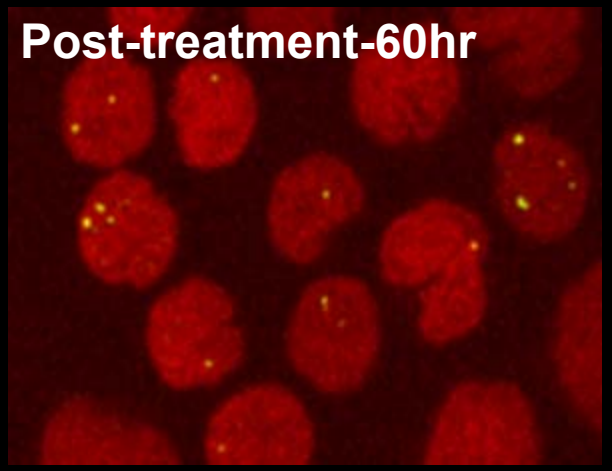
Post-treatment-24hr



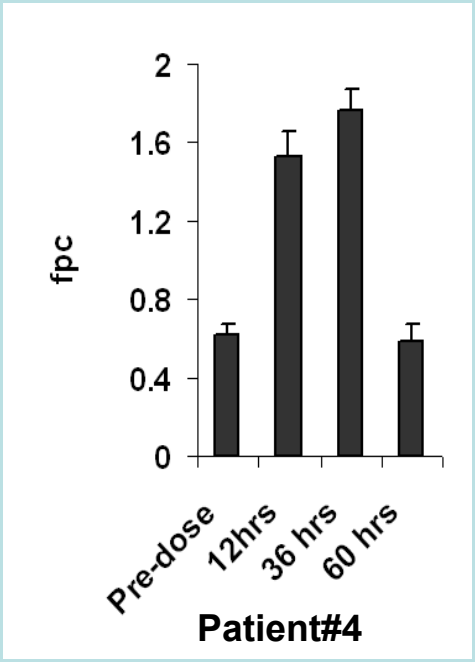


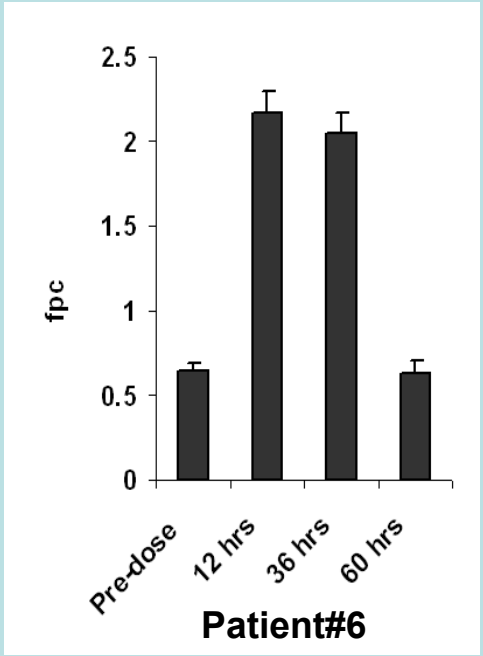




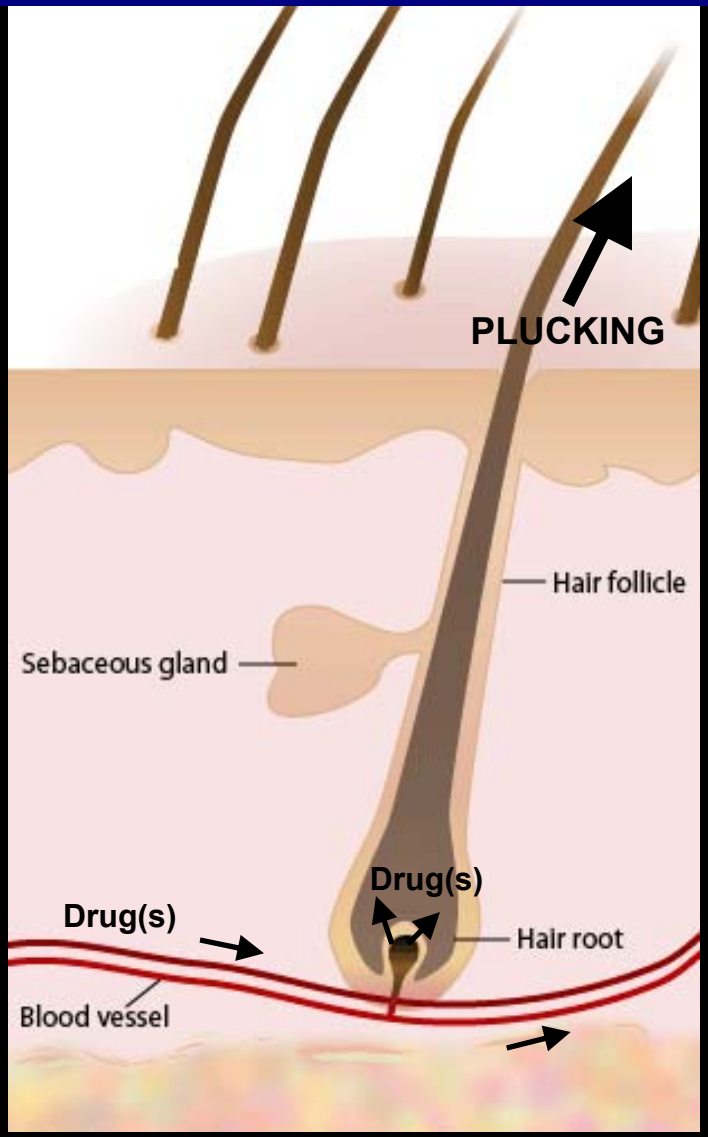


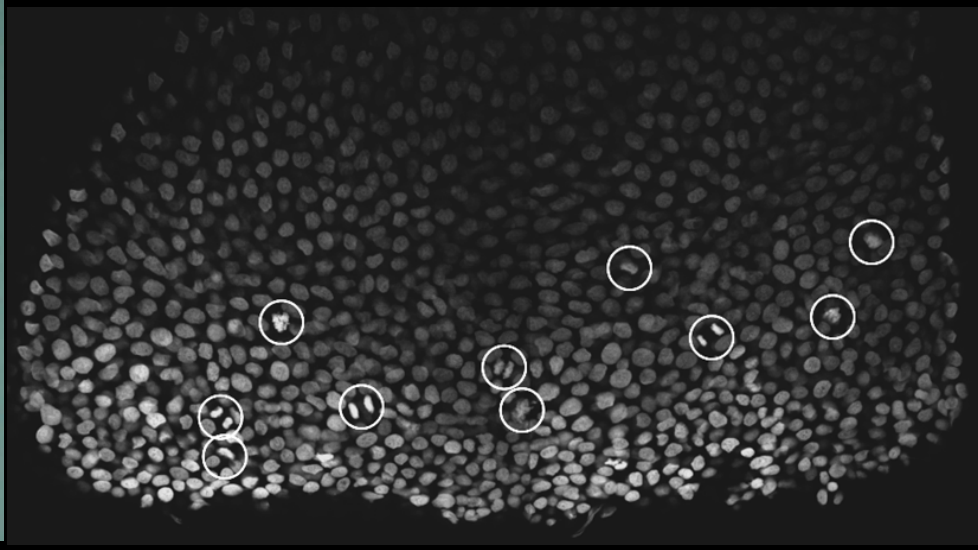
Lymphocytes – Drug combination

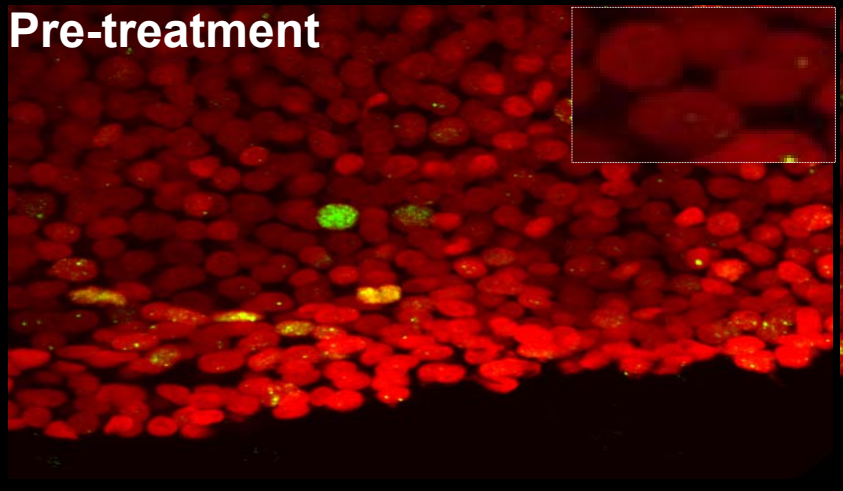


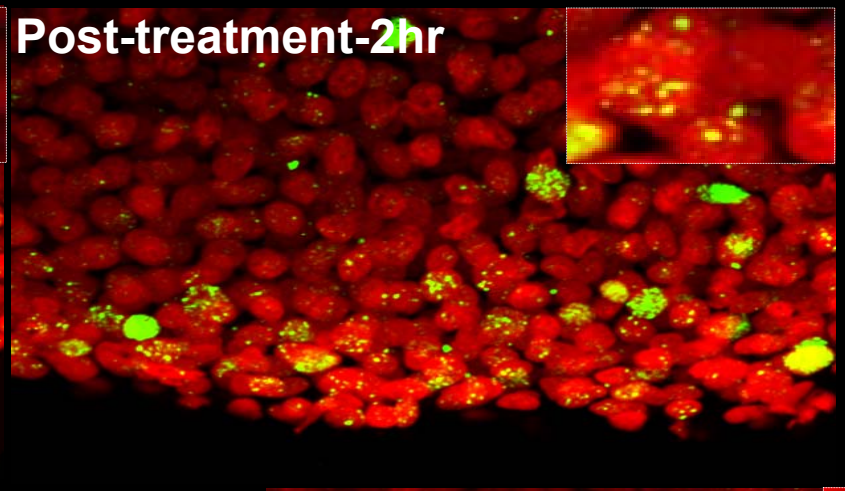


Drug delivery in organs: hair follicles

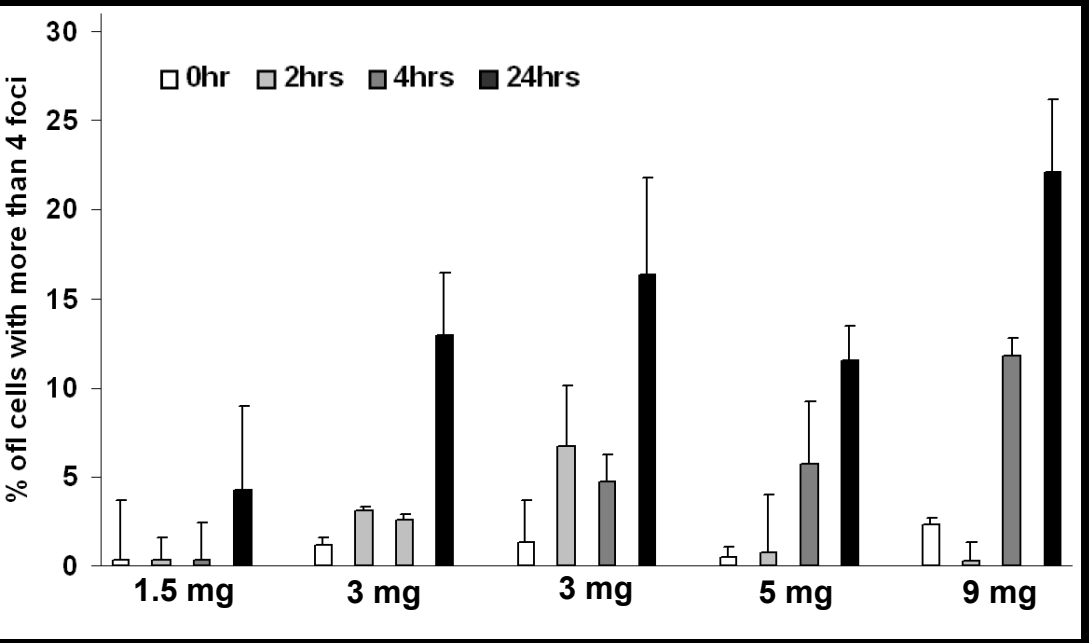


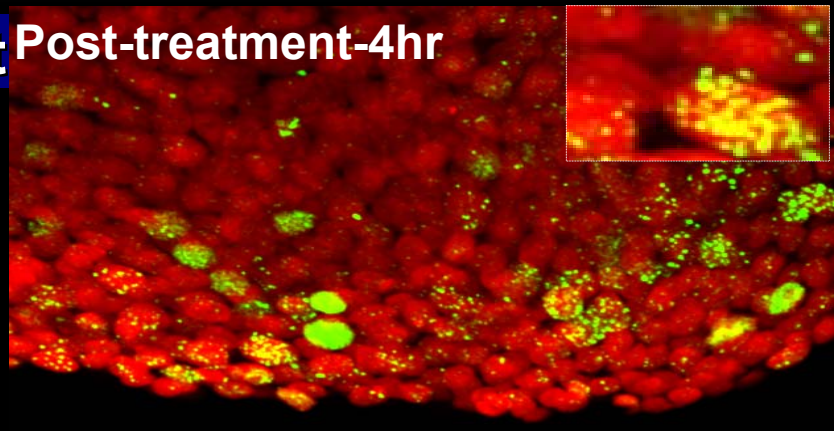


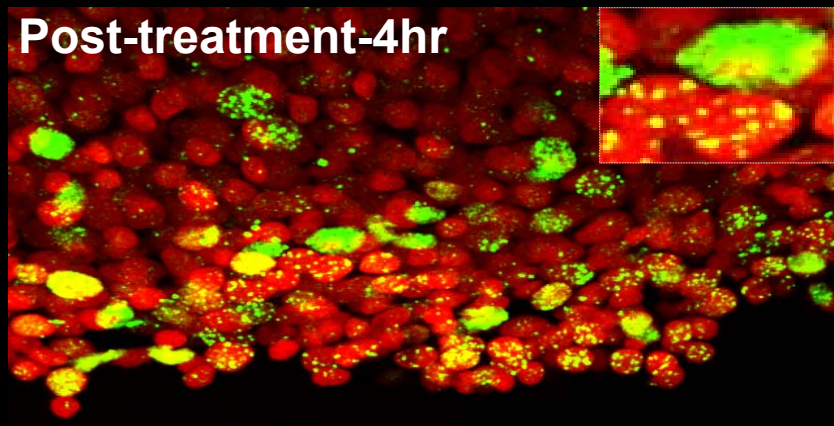




Plucked hairs - DNA alkylating agent







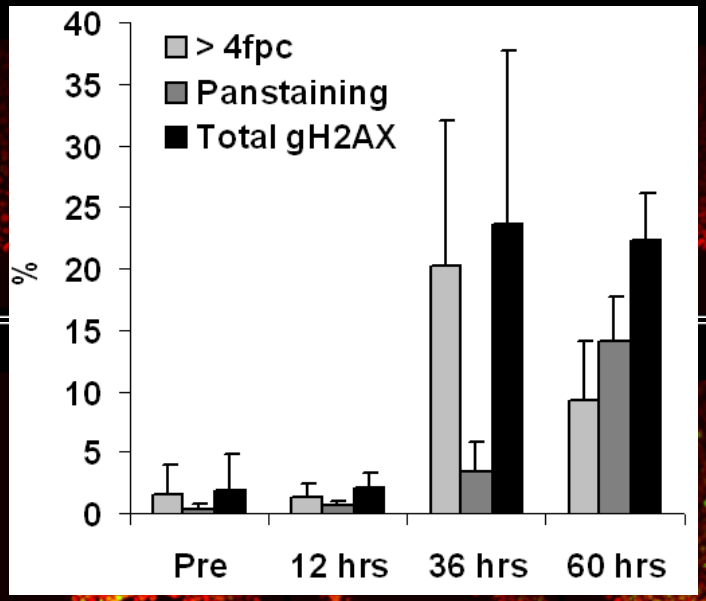
Hairs - Drug combination

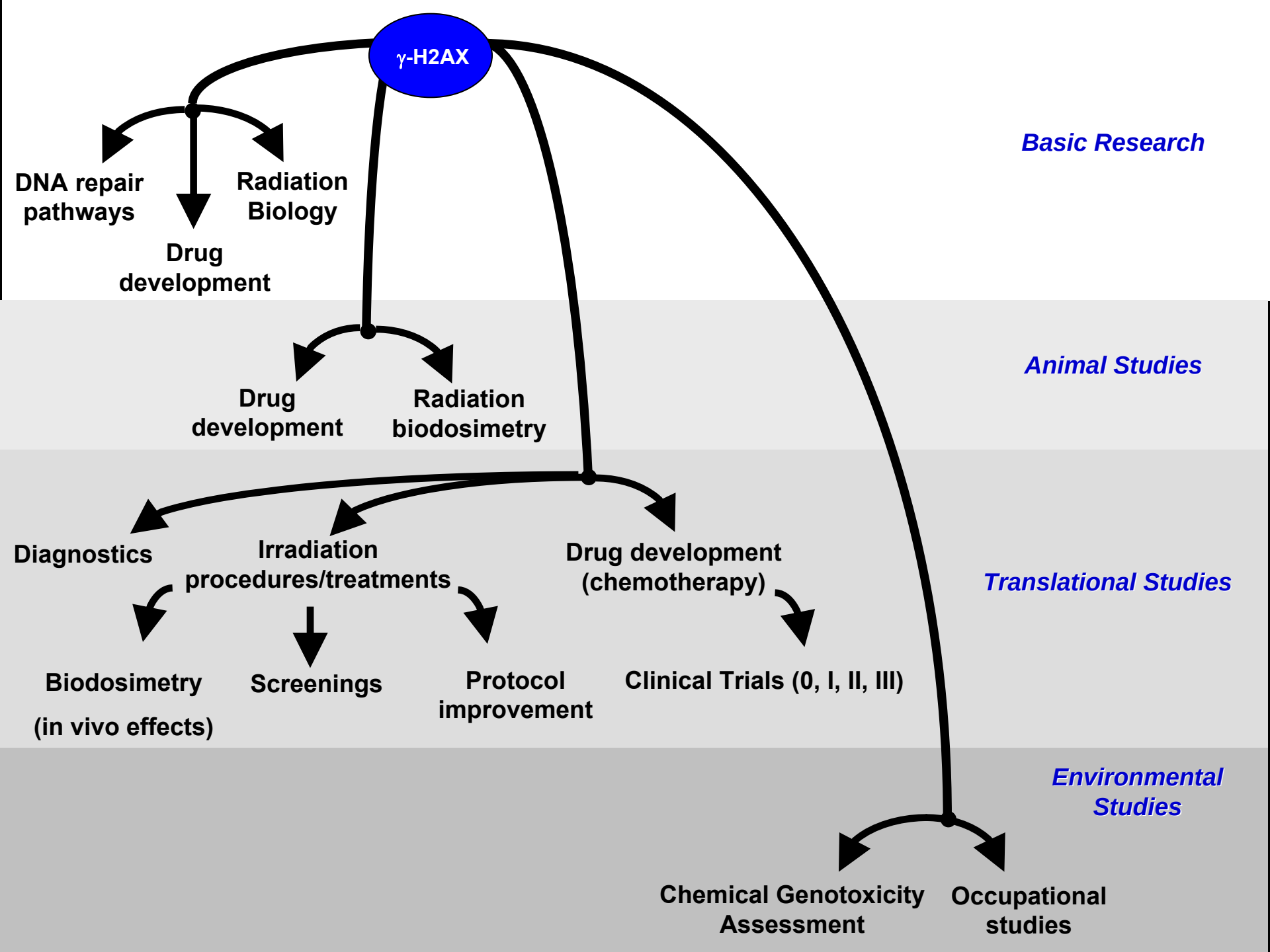
Pre-treatment

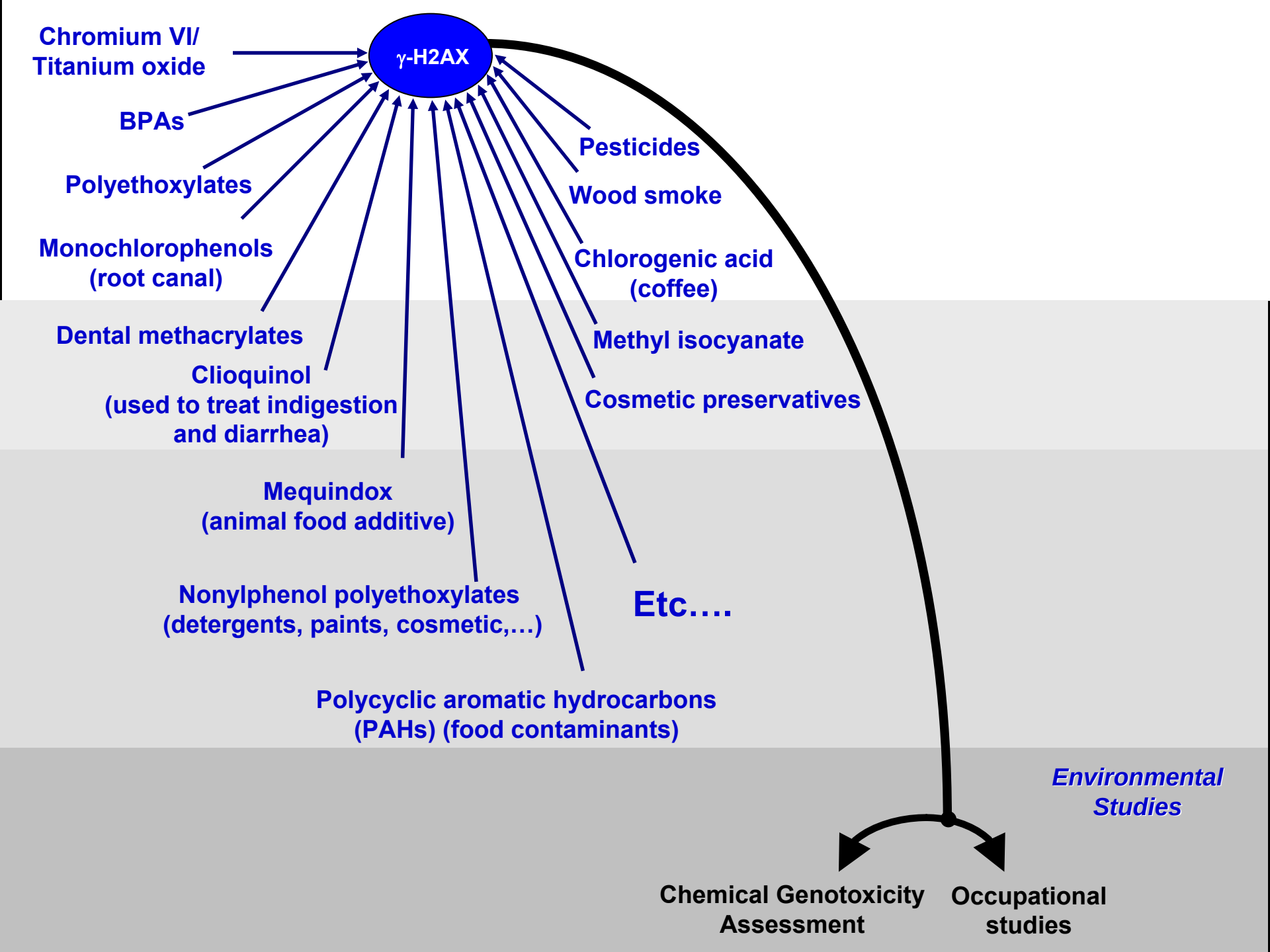
12 hr

36 hr

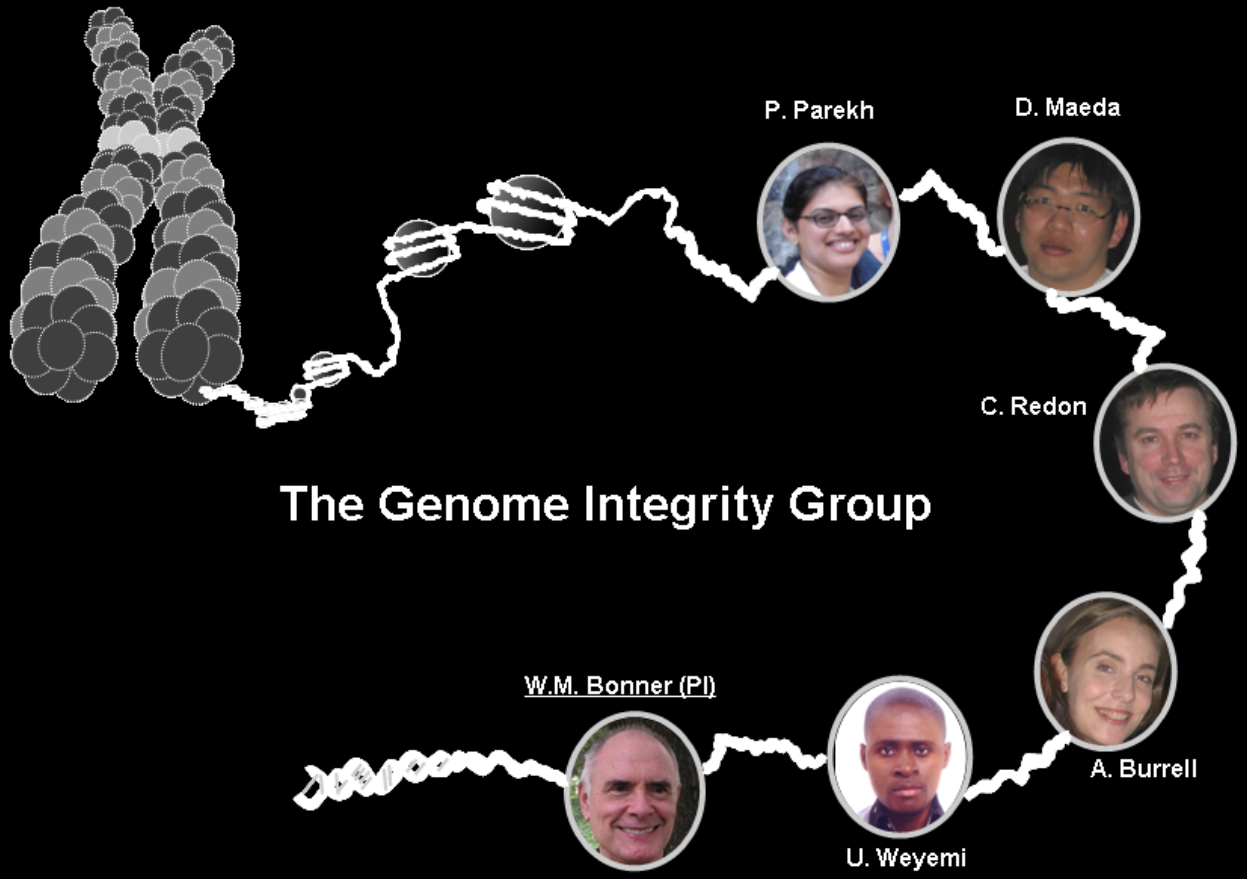
60 hr




γ-H2AX
DNA repair pathways
Drug development
Radiation Biology
Basic Research
Drug development
Radiation biodosimetry
Animal Studies
Diagnostics
Irradiation procedures/treatments
Drug development (chemotherapy)
Translational Studies
Biodosimetry (in vivo effects)
Screenings
Protocol improvement
Clinical Trials (0, I, II, III)
Environmental Studies
Chemical Genotoxicity Assessment
Occupational studies


Chromium VI/
Titanium oxide
BPAs
Polyethoxylates
Monochlorophenols
(root canal)
Dental methacrylates
Clioquinol
(used to treat indigestion
and diarrhea)
Mequindox
(animal food additive)
Nonylphenol polyethoxylates
(detergents, paints, cosmetic,…)
Polycyclic aromatic hydrocarbons
(PAHs) (food contaminants)
γ-H2AX
Pesticides
Wood smoke
Chlorogenic acid
(coffee)
Methyl isocyanate
Cosmetic preservatives
Etc….
Environmental
Studies
Chemical Genotoxicity
Assessment
Occupational
studies

Thank you


P. Parekh
D. Maeda
C. Redon
The Genome Integrity Group
W.M. Bonner (PI)
A. Burrell
U. Weyemi